Chapter 7

Biomarker-Based Targeted Therapeutics

Shainan Hora, Amit Kumar Pandey and Sudhakar Jha

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78377

Abstract

Cancer biomarkers are emerging as important tools for disease diagnosis, prediction and prognosis. A significant number of studies have been reported in the field of biomarker discovery due to their potential as personalized targeted therapy. With the converging gap about their utilization as specific targets, studies have focused on identifying disease-specific biomarkers in different cancer types. This chapter provides a comprehensive overview about different cancer-associated biomarkers, their prevalence in different cancer types and their use as targeted therapy. Additionally, we provide an in-sight on the therapeutic and diagnostic potential of different noncoding RNAs as cancer biomarkers.

Keywords: biomarkers, exosomes, chemokines, noncoding RNA, therapeutics

1. Introduction

Cancer is a genetic disease with great molecular diversity and unpredictable nature, which makes it complicated to generate reliable therapeutic interventions for treating cancer. Current treatment strategies include chemotherapy, radiotherapy and surgery. Cancer patients often show primary resistance to directed therapy or often develop adaptive resistance during the course of treatment. Hence it is extremely important to understand the molecular basis of cancer and search reliable biomarkers that can be employed in field of cancer diagnosis and treatment.

Precision medicine, classified as personalized cancer therapy, has increased our knowledge of aberrantly regulated genes and their involvement in tumorigenic pathways towards developing better therapeutic strategies. The advancement in information about the cause and effect of cancer genetics has translated to personalized targeted therapy, one such based on cancer

biomarkers. A biomarker is defined as biological molecule such as a protein, DNA, RNA or circulating extracellular vesicles (EVs) that can be found in blood, biological fluids and tissues and is an indicator of a normal physiologic or a diseased state. Cancer biomarkers are predictive of altered gene signature marks at the transcription level and/or of abnormal proteomic or metabolomic patterns. These biomarkers are used for molecular diagnosis, patient prognosis and to determine the outcome of the targeted therapy. Hence, it is extremely important to understand the evolving landscape of cancer genetics and to combine tumor aberrations with personalized biomarker-based targeted therapy.

Human genome sequencing has identified approximately 30,000–40,000 genes and only 2–3% of the coding sequence of the genome are evolutionary conserved among mammals [1, 2]. About 98% of genome sequence was initially classified as junk DNA, but recent progress in deep sequencing has discovered these to be transcribed as noncoding RNAs (ncRNAs). These ncRNAs are grouped as different types of functional RNAs, such as Piwi-interacting RNA (piRNA), microRNA (miRNA), small nucleolar RNA (snoRNA), circular RNA (circRNA) and long noncoding RNA (lncRNA). ncRNAs have been shown to affect gene expression and disease progression, making them important targets for drug discovery. Clinically, aberrations in ncRNAs show high prognostic and diagnostic importance. With the advancement in technology and enhancement in understanding the nature of ncRNAs, novel therapeutic treatments against cancer can be developed.

This chapter focuses on deciphering a comprehensive approach on the recent biomarkers that are available as therapeutic options, their scope, utility and implementation as prognostic and diagnostic tools for cancer therapy. We will focus on role of ncRNAs and discuss their potential use as a prognostic and diagnostic marker in various cancers. We will also address the challenges and possible solutions in their assessment as biomarker for therapeutic use.

2. Cancer biomarkers

A biomarker is a collection of genetic and proteomic signatures used to distinguish between healthy and diseased individual. These signatures can be in the form of DNA (ssDNA, dsDNA and retrotransposons), RNA (mRNA, miRNA, circRNA and lncRNA) or protein (antibodies and peptides) depending upon the site of secretion and isolation [3]. A biomarker is predictive of disease prognosis and prediction, risk of recurrence or to determine the therapeutic potential of an identified target. The success of biomarker-based therapy can be attributed to the development of new sequencing strategies and characterization of tumor pathways with increasing knowledge about druggable targets and its predictive outcome. One of the earliest biomarkers to reach clinical practice was the identification of mutations in *KRAS* gene in case of metastatic colorectal cancer (CRC), which was predictive of therapeutic response towards anti-epidermal growth factor receptor (EGFR) [4]. However, owing to the heterogeneity of tumor cells, lack of information on specific biomarkers associated with particular disease type (and subtype) and different developmental strategies, biomarker-based therapy has not fully transcended to clinical stages.

Cancer biomarkers are broadly categorized into three divisions based on the specific signature it is associated with: diagnostic, predictive and prognostic biomarkers [5]. As the name

suggests, diagnostics biomarkers predict disease outcome associated with a particular malignancy; predictive biomarkers predict the success of a particular therapeutic strategy applied to treat the disease followed by prognostic biomarkers that predict the risk of disease recurrence in the future. Currently, there are only a handful of FDA approved biomarkers in the market highlighting the present-day challenges, starting from their diagnosis to clinical approval. Some examples of FDA approved biomarkers include: HER2 overexpression as a predictive marker to determine the survival status of breast cancer patients treated with anti-HER2 therapy [6]. Another example of FDA approved diagnostic maker include testing the patients suspected with prostate cancer for the prostate-specific antigen (PSA) to test for malignancy of the associated disease (recent studies have found PSA screening to be inconsistent [7] however, further studies needs to be done to understand the discrepancy). Measurement of 70-gene expression analysis used to predict the recurrence of breast cancer after chemotherapy, is an FDA approved prognostic biomarker-based assay [8]. Apart from the FDA approved biomarkers, there are various new approaches being utilized towards personalized targeted therapy so as to bridge the gap between disease diagnosis and its clinical manifestation.

This section will discuss different types of biomarkers characterized thus far in different cancers; their scope and utility for targeted therapy and will provide an overview of the new biomarkers being identified and their possible translational to clinical levels (**Figure 1**).

2.1. Extracellular vesicles as biomarkers of cancer

Tumor cells are characterized by a neoplastic set of population that continuously divides and evolves into sub-population of cells, each with its own heterogeneity. Among the many reasons for cancer therapeutics failure, one of them is the associated tumor heterogeneity and despite the new sequencing strategies developed, there are major challenges that need to be

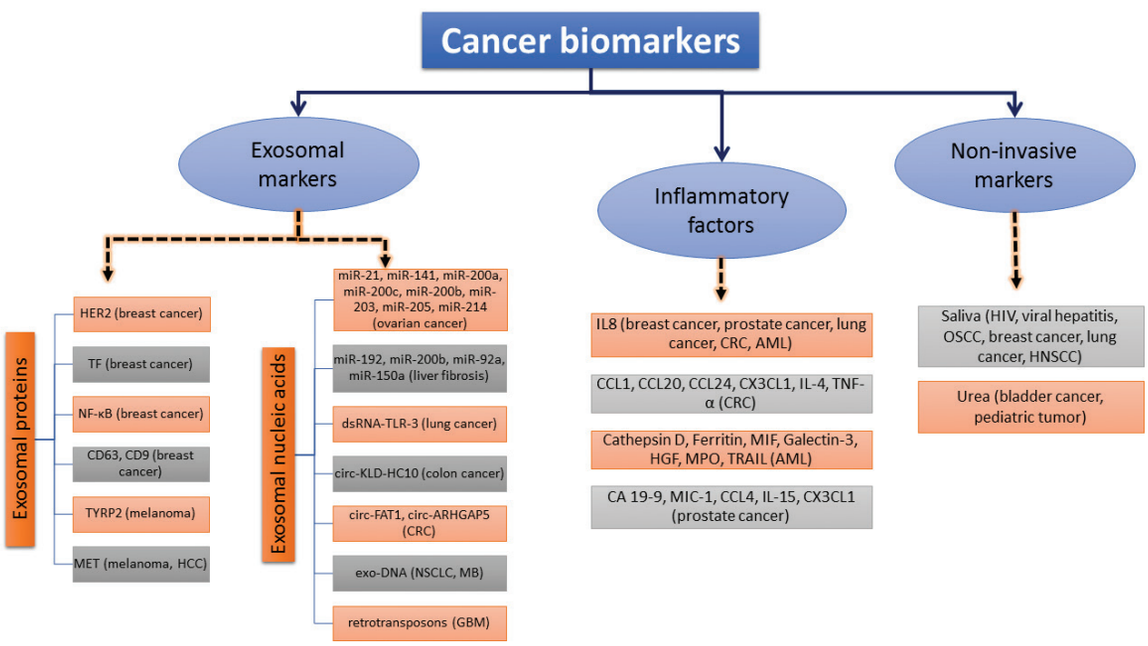

Figure 1. Different cancer-associated biomarkers. An overview of the different biomarkers associated with specific cancer types. Targeting these biomarkers could serve as important therapeutic option for associated malignancies (abbreviations as used in the text).

overcome. Studies have found that tumor cells secrete EVs such as exosomes and macrovesicles into the extracellular environment at a threefold higher rate than normal cells [9, 10]. These vesicles carry important genetic information such as DNA and RNA or protein fragments that act as signatures of the secretory cell type [11]. Identification of EVs from patient's blood stream, urine or plasma provide important insights into the cells they originate from, their genetic constituent and molecular variants. Identification of EVs as potential biomarkers along with the advancement in techniques for their successful isolation has enabled new therapeutic targets for cancer treatment. EVs are isolated from the conditioned media of cells *in vitro* or from biological fluids such as serum and plasma of patients. Some of the important identified secretory signatures in patient-derived vesicles known so far include receptor of a hepatocyte growth factor (HGF) identified in melanoma called MET [12], miRNAs in ovarian cancer [13] and in breast cancer the human epidermal growth factor receptor 2 (HER2/neu) [14] among many. EVs affect the cell milieu by enabling transfer and exchange of important information among different cell types, pre-metastatic niche formation and triggering cell type specific inflammatory immune response [15].

EVs are sub-classified into exosomes, macrovesicles and large oncosomes based on their size. Of these, exosomes (30–120 nm in diameter) are widely considered a valuable source of biomarkers [16] and as important mediators of biological information. Exosomes are bilayered membranous structures comprising of various lipids and proteins, are formed from intracellular vesicles and release their content extracellularly (outside the cell) [17]. Cancer cells secreted exosomes affect the microenvironment not only of the proximally located cells, but also cells of distal origin [18]. Information carried by exosomes not only plays significant role in normal pathological processes, but are also a hallmark of aberrantly regulated pathways in different cell type-associated malignancy. Exosomes have also been characterized as 'liquid biopsy' tools [19] owing to their stability in secreted bodily fluids such as plasma, urine or saliva. Various exosomal markers such as CD63, TSG101 and Alix, among many are known and their detection from conditioned media of cancer cells or from patient-derived tumor samples gives an indication of diseased process [20]. These specific protein markers allow for their characterization as specific liquid biopsy tools in cancers of different origin.

2.1.1. Exosomal proteins as cancer biomarkers

Various studies have reported that secretory information from exosomes could serve as a diagnostic tool in identification of breast cancer types. For example, in secretory exosomes of some breast cancer cell lines, which overexpressed HER2, full-length HER2 protein levels were found to be overexpressed when compared to normal cells [14]. It was found that in EGF (a ligand for HER2)-treated cells, the release of exosomes was higher as measured by the cell-conditioned media and could serve as an important predictive tool in HER2-driven tumors. Monitoring the status of HER2 in blood-derived patient exosomes could therefore serve as a diagnostic tool in breast cancer and to improve the disease outcome. Another study found that a blood clotting specific protein called tissue factor (TF) correlated to increased tumor invasiveness in breast cancer by its incorporation into tumor-derived EVs [21]. TF-derived EVs from highly metastatic triple negative cell line MDA-MB-231 was transferred to less aggressive MCF-7 cell line. It was observed that increased levels of incorporated TF associated with

more aggressive phenotype was responsible for cancer-associated thrombosis. Circulating exosomal vesicles are known to be upregulated during cancer progression and are associated with intercellular communication. A study found that breast cancer-derived exosomes from MDA-MB-231 (MDA-231) and MCF7 cells had elevated levels of transcription factor nuclear factor-κB (NF-κB) and its associated activation of signaling pathway in the macrophages as compared to exosomes from MCF10A cells. Increased NF-κB signaling led to increased production of pro-inflammatory cytokines, which included factors such as interleukin-6 (IL6), granulocyte-colony stimulating factor (GCSF), chemokine ligand 2 (CCL2) and tumor necrosis factor α (TNFα) [22]. The increased inflammatory response in the macrophages contributed to metastatic niche formation and to modulate immune cells activity. Thus, targeting the activity of NF-κB pathway could be used as a therapeutic option to block the secretion of exosomes and consequently the formation of metastatic microenvironment. EVs from brain metastatic cells were found to be within 100 nm diameter size and expressing markers such as CD63 and CD9, characteristic of exosomes [23]. A study found that breast cancer-derived exosomes contribute to the breakdown blood-brain barrier (BBB) and *in vivo* cell metastasis in the brain [23]. Secretion of exosomes was inhibited by targeting the degradation of EV proteins involved in its biogenesis such as neutral sphingomyelinase (nSMase2) and RAB27B. It was found that cells showed reduced migratory potential and that its migratory ability was restored when exosomes derived from breast cancer cells was added. Thus, targeting the cancer-derived exosomes could be an important therapeutic option for the prevention of BBB breakdown and to prevent its associated malignancies.

In another study, exosomes were isolated from the plasma of the patients with tumor grade I–IV [12]. It was found that patients with high exosomal proteins in stage IV had low survival rate as compared to patients in the same stage with low exosomal proteins content. Along with this, increased levels of specific melanoma protein, tyrosinase-related protein-2 (TYRP2) [24] was seen in exosomes isolated from melanoma cell lines. Levels of TYRP2 in exosomes of patients also correlated to their increased metastatic progression of tumors. Given the increasing studies on exosomal horizontal transfer of molecules [25] and intercellular communication, it was hypothesized that an oncogenic protein known to be metastatic could play a role. Among the different known proto-oncogenes such as MET, CD44, Annexin A6 and Hsp70 [26, 27], MET was considered a possible target owing to its role in invasion and metastasis [28]. It was found that in melanoma cell-derived exosomes, secretory vesicles could horizontally transfer MET to bone marrow-derived cells and that the levels of MET and phospho-MET (p-MET) protein was eventually found to increase in exosomes of these cells. Subsequently, MET and p-MET levels was also found to be high in circulating exosomes isolated from patients with stages III and IV grade melanoma. Hence, it was hypothesized that targeting MET protein using specific inhibitors could provide new opportunities to restrict the metastatic progression of cells in tumors. A similar study on exosomes isolated from hepatocellular carcinoma (HCC) cell lines showed MET proto-oncogene isolated from metastatic HCC cell line to increase the migratory potential of non-motile HCC cells [29]. The uptake of exosomes harboring MET protein in the cells triggered PI3K/AKT and MAPK signaling pathways [30] leading to increased metastatic potential of cells. Increased MET and p-MET along with increased p-AKT and MEK1/2 phosphorylation as well as levels of MMP2 and MMP9 were confirmed in the conditioned media of immortalized HCC cells after exosome

treatment from metastatic cells. Data were correlated with that obtained from HCC patients, where aberrant activation of MET/HGF pathway signaling pathway corresponded to poor prognosis and survival [31].

2.1.2. Exosomal nucleic acids as cancer biomarkers

First evidence of exosomal shuttle RNA (esRNA) came from a study which found that exosomes harbor both mRNA and miRNA and that they are involved in intercellular communication [11]. It was found that mRNA and miRNA secreted from mast cells were packed into exosomes and the coding information on mRNA could be translated into protein. The exosomes containing translatable information could be transferred between cell types, thus providing important insights and complexity in which the information is relayed. Targeting the exosomal RNA, that is shuttled between the cells, could therefore allow for targeted therapies in cell type-associated cancer. Subsequently, it was found that in ovarian cancer patients, levels of eight specific miRNAs obtained from exosomes were similar to that obtained cellularly. These circulating exosomal miRNAs isolated from serum samples include miR-21, miR-141, miR-200a, miR-200c, miR-200b, miR-203, miR-205 and miR-214 [13]. This suggests the importance of profiling circulating miRNAs from diseased patients and their use as important diagnostic tools and as liquid biopsy markers. A similar study based on identification of miRNA levels, found different miRNAs in the EVs isolated from the plasma of the patients infected with HBV or HCV infection. Expression profile of miRNAs isolated from circulating vesicles showed reduced miR-192, miR-200b, miR-92a and miR-150a levels [32]. Thus, miRNAs expression levels can be correlated to early stage liver fibrosis identification. Lipid bilayered vesicular contents of exosomes are recognized by multiple pathogen recognition receptors (PRRs), which include retinoic acid-inducible gene I (RIG-I) and toll-like receptors (TLRs) – TLR2, and TLR4 among others [22]. A study found that tumor-derived exosomes stimulated the activation of TLR3 in alveolar epithelial cells followed by the production of pro-inflammatory cytokines and pre-metastatic niche formation [33]. Since TLR3 recognizes dsRNA, RNA isolated from tumor-derived exosomes upregulated the expression of TLR3, thereby leading to cytokine production by activation of downstream NF-κB and MAPK pathways [34]. Activated TLR3 also led to the recruitment of neutrophils in the lungs, which elicited a pro-metastatic inflammatory response. Thus, insights into tumor-derived exosomal RNAs could provide important clues to target tumor metastasis in the lungs.

The first evidence of Exo-circRNA (circular RNA from exosomes) came from a study which showed them to be enriched at a twofold higher rate in liver cancer cells as compared to circRNA present in those cells [35]. Data from RNA-seq showed abundant circRNA in liver cancer cells as compared to normal cells. It was found that levels of these identified circRNA were about sixfold higher than linear RNA in the exosomes of these cells. The researchers further investigated whether serum from cancer affected patients were enriched with circRNA. Serum from patients with colon cancer showed high levels of an exo-circRNA, circKLD-HC10 in the exosomes of patients in comparison to healthy controls. This was the first evidence of exosome-based circular biomarkers as potential therapeutic options. In another study based on circRNA, expression profile of circRNAs present in both cells and exosomes of different

CRC cell lines that differ in the KRAS mutation status were analyzed [36]. KRAS is a proto-oncogene first identified in Kirsten rat sarcoma virus [37] and whose mutation or upregulation is associated with cancer progression based on the different pathways it acts upon. It was found that in cells where KRAS was mutated, a number of circRNA isolated from exosomes were downregulated as compared to those identified in cells having wild-type KRAS allele. These circRNAs include circFAT1 and circARHGAP5. To further investigate the reason for their downregulation, levels of known regulators of circRNA, adenosine deaminases acting on RNA (ADAR, an RNA editing enzyme) [38] and quaking (QK1, an RNA binding protein) [39] were determined. It was found that decreased levels of above-mentioned circRNAs directly correlated to decreased levels for QK1 found in the mutant cells. Levels of circRNAs could therefore serve as important biomarker for disease prediction.

The first report of tumor-derived exosomal DNA (exoDNA) showed that exosomes carried double-stranded DNA (dsDNA). The levels of these exoDNA corresponded to the mutational status of cancer cells and can therefore be used as an important circulating biomarkers in case of cancer-associated metastasis [40]. Mutation status of different genes known to be mutated in cancer cell lines were determined to see if the status of the genes corresponded to that obtained from exoDNA. It was found that BRAF allele was mutated in exoDNA in primary human melanoma cells containing BARF mutation as compared to cells that did not harbor the mutation. Also, status of EGFR, which is known to be mutated in case of non-small cell lung cancer (NSCLC) [41], was determined and same observation as compared to BRAF allele was found, confirming that exoDNA shows the same mutation status as that in parental cells. This shows that, exoDNA reflects the genomic status of the DNA present in cancer cells and because it is stable and feasible to isolate, could serve as an important biomarker. In addition to the dsDNA found in exoDNA, another study found the presence of ssDNA in the microvesicles (another subclass of extracellular vesicles with 30 nm–1 μm in diameter) from the tumor cells in culture in addition to retrotransposon elements [42]. Nucleic acids were identified from microvesicles released by cells *in vitro* and from tumors. It was found that along with RNA, ssDNA in the form of exoDNA as well as transposable elements were present in the microvesicles. Levels of exo-RNA were found to be higher in medulloblastoma (MB) cells, which released more microvesicles as compared to normal cells with intact 18S and 28S ribosomal peaks. Similarly, in MB cells levels of exoDNA was found to be more abundant as that in normal cells and was found to be single stranded. The strand status was confirmed using a detection chip that detected only dsDNA (the isolated single-stranded exoDNA was subjected to second strand synthesis, which converted it into double-stranded form and hence was detected by the chip). Retrotransposons such as human endogenous retroviruses (HERVs), long interspersed nuclear element-1 (LINE-1) and Alu were found to be enriched in microvesicles isolated from glioblastoma (GBM) cells. RNA from these transposable elements were enriched as compared to their cellular levels in these cells. Interestingly, experimental observations also suggested that HERV RNA is elevated in endothelial cells when these were exposed to microvesicles from tumor cells, indicating that these retrotransposons (jumping genes) could lead to genomic instability. Taken together, this study reveals that the uniquely identified retrotransposons RNA could serve as important biomarkers in tumor cells along with DNA from patient-derived body fluids. Additionally, the level of these retrotransposons could be an important indicator of the cell type-specific tumor origin [43].

2.2. Inflammatory cytokines and chemokines as biomarkers of cancer

Levels of invading microbial pathogens during an inflammatory response are regulated by the first line of immune defense called the innate immune system [44]. The pathogen-associated molecular patterns (PAMPs) are bound by the associated PRRs, each recognizing its own unique set of patterns [45]. Upon receptor activation, a pro-inflammatory and antimicrobial response is triggered in the host system, which includes a series of signaling events comprising of small molecules, transcription factors and kinases [46]. Subsequently, the signaling pathways relay the signal activating the associated cytokines or chemokines of the pathway [45], which generate a long-term response, ultimately leading to the activation of adaptive arm of the immune response.

Cytokines and chemokines are key modulators of inflammation and are involved in a variety of diseased processes based on their specific role. These can be pro- or anti-inflammatory, depending upon their class and type. For example, certain pro-inflammatory cytokines include interleukins (IL) such as IL-1, IL-6, TNFα and interferons (IFNs) among many [47]. Examples of anti-inflammatory factors include IL-12 and IL-10 among many [47]. Chemokines are small group of proteins characterized by conserved cysteine residues that recruit leukocytes to the site of inflammation. Common chemokines include any protein with a CCL or CXC motif such as RANTES (CCL5) and IL8 (CXCL8) among many [47]. The level of cytokines and chemokines differ greatly among individuals depending upon normal or diseased outcome. The downstream effects produced by these inflammatory regulators depend on the signaling pathway activated, their targets and the associated patterns. Although these factors are involved in many disease-associated processes, their levels are not consistent across similar diseased processes. The variation is due to the difference in their cut-off levels on what is considered normal versus abnormal [48] as well as the population size of the cohort used in the study (healthy or diseased) [49]. Hence, it is difficult to characterize them as unique biomarkers or as diagnostic tools for any cytokine-associated specific disease. Despite these limitations, considerable progress has been made and recent studies have focused on important cytokines and chemokines, their involvement in cancer-associated diseases and their use as cancer biomarkers.

2.2.1. IL8 as a cancer-associated biomarker

IL8, a 6–8 kDa pro-inflammatory chemokine is the most widely studied for its role in recruiting neutrophils to the site of infection, activation of angiogenesis and metastasis [47]. Many metastatic and tumors of breast, prostate and colon cancer are known to constitutively express IL8 [50]. IL8 ligand is bound and recognized by its G-protein coupled receptors (GPCRs) CXCR1 and CXCR2, with CXCR1 being the more specific receptor for mediating the response [47]. A number of therapeutic strategies therefore utilize the difference in pharmacological properties of these receptors to target and attenuate the effect of IL8 on the tumor microenvironment. High serum levels of IL8 correspond to poor prognosis and increased metastasis as seen in patients with metastatic breast cancer [51]. It was also noted that in cells treated with cytotoxic agents, IL8 levels were high with increased chemo-resistance observed in tumor cells. Another study on breast cancer found the role of a protein of *Drosophila* gene called dachshund (dac) to be important in patient prognosis [52]. *Drosophila dac* gene is involved in differentiation [53] and is a founding member of the human homolog *dac* protein DACH1, a

cell fate determination factor [54]. Levels of DACH1 directly correlated to patient survival and were found to be low in metastatic breast cancer. It was found that DACH1 inhibited cell migration and invasion by decreasing the levels of IL8 in breast cancer cells. DACH1 repressed the IL8 promoter in a dose-dependent manner by occupying the AP-1 and NF-κB sites. Adding neutralizing antibody against IL8 resulted in a decrease in the migratory potential of the cells, showing that targeting IL8 as a biomarker could be a potential mechanism to inhibit cell growth.

In addition to binding to its own receptor, IL8 binds and upregulates the expression of another receptor, CXCR7 in case of prostate cancer leading to cell proliferation and growth [55]. It was observed that CXCR7-mediated growth was dependent on the activation of EGFR and independent of its own ligand, highlighting the importance of targeting CXCR7 as a potential biomarker along with IL8 in case of prostate cancer. In case of lung cancer, a study found that high circulating levels of IL8 were predictive of the risk of lung cancer in patients prior to diagnosis [56]. Along with IL8, IL6 was also found to be predictive of the high risk of lung cancer but only in cases within 2 years of blood collection. However, highest associated risk of lung cancer was determined in patients with several years of smoking habit and showed high IL8 and C-reactive protein (CRP) levels. Thus, plasma levels of IL8 along with CRP could be a more robust predictor of lung cancer (several years before diagnosis) for tumor progression and relapse.

Promoter methylation is often characterized with aberrant transcriptional regulation and/or tumor suppressor genes silencing [57]. It was found that in MDA-231 and MDA-MB-435 (MDA-435), two highly metastatic breast cancer cell lines that produce high levels of IL8, two CpG sites were methylated 1.2 kb upstream of IL8 promoter. The observed methylation pattern showed a positive correlation with IL8 expression, suggesting additional uncharacterized epigenetic control known so far [58]. Similar approach in CRC was taken and it was observed that IL8 promoter was hypomethylated in 64% of tissue samples [59]. Hypomethylation of the promoter led to high IL8 protein levels and associated metastasis, showing that high IL8 levels along with hypomethylated IL8 promoter, could be a useful marker for disease progression. Despite the vast array of information on IL8 and its role in different cancer progression and metastasis, only handful inhibitors against it are used in preclinical studies and even few have reached clinical trials. Neutralizing antibodies against IL8, ABX and HuMax are being used to block the binding to IL8 to its receptor [60]. ABX has shown to reduce tumor growth in mice in case of bladder cancer [61] and reduction in metastasis and angiogenesis along with reduced tumor size in case of melanoma [62]. Reparixin, an inhibitor of IL8 receptor CXCR1/2 is in clinical trials for the treatment of patients affected with HER2-negative breast cancer and patients with TNBC along with paclitaxel (an FDA approved microtubule-stabilizing drug for ovarian, breast and lung cancer treatment [63]).

2.2.2. Other inflammatory factors as cancer biomarkers

In a study on colorectal cancer patients (stages I–IV grade), levels of inflammatory factors were determined in the blood at the time of surgery [64]. It was found that CRC-specific mortality directly correlated to the plasma levels of various inflammatory factors. In particular, levels of IL-4, TNFα, CCL1, CX3CL1, CCL20 and CCL24 were upregulated in patients with CRC-specific mortality. Thus, high levels of these inflammatory cytokines, chemokines

and interleukins found in the plasma of affected individuals could be a diagnostic marker to determine disease outcome and prognosis. A study on acute myeloid leukemia (AML) reported a cohort of seven inflammatory molecules to be upregulated and predictive of AML diagnosis irrespective of the disease heterogeneity [65]. These molecules include Cathepsin D, Ferritin, Macrophage migration inhibitory factor (MIF), Galectin-3, HGF, myeloperoxidase (MPO) and IL8 suggesting that their plasma levels could be predictive of disease diagnosis. In accordance with the TCGA database, levels of two other novel inflammatory molecules TNF-related apoptosis-inducing ligand (TRAIL) and MIF were downregulated and upregulated, respectively, in the plasma of patients. Levels of MIF correlated with that found in other cancer types such as prostate and breast and is known to activate PI3K/Akt pathway, leading to anti-apoptosis and survival [66]. Thus, along with the seven biomarkers for prognosis, MIF could serve as an important therapeutic target in AML.

Carbohydrate antigen (CA) 19-9, is the only FDA approved diagnostic marker for prostate cancer but its diagnosis is limited due to inaccurate sensitivity and specificity in different prostate cancer subtypes [67]. There is thus an ardent need for a personalized biomarker predictive of disease outcome. A study found the levels of macrophage inhibitory cytokine 1 (MIC-1), a novel TGF-β superfamily cytokine [68] in patient serum affected with prostate cancer, to be differentially expressed in comparison to healthy cohorts [69]. The diagnostic sensitivity and specificity percentage of MIC-1 from a total pool of different prostate cancer patients were found to be low but improved significantly when both CA 19-9 and MIC-1 were detected in patient serum [70], showing that these biomarkers together could be used as diagnostic tools in prostate cancer. Another example of the use of multiple biomarkers for patient prognosis and disease outcome in prostate cancer came from a study which identified three inflammatory factors in tissue samples of patients post prostatectomy [71]. Among the 30 cytokines that were measured, the expression levels of CCL4, IL-15 and CX3CL1 were significant and were predictive of recurrence free survival 5, 3 and 1-year post surgery.

2.3. Noninvasive cancer biomarkers

Research on biomarkers and its clinical translation is still in its early phase despite the recent advances in the field. This is due to the complexity in identifying the specific biomarker, its sensitivity of prediction and the isolation method used. There is therefore a need for the development of a noninvasive, inexpensive and accessible biomarker to evaluate disease progression and for better diagnosis. Besides the use of bio-fluids such as saliva and urine for basic health assessment, they are being used to monitor disease progression and possible outcome. The progress in the usage of saliva as a diagnostic biomarker fluid can be attributed to its FDA approval in 2003 for detecting HIV infection. In case of HIV, levels of a microglobin B2M b2, an end product of increased cytokine production and a soluble tumor necrosis factor α-receptor 11 (sTNFαR11) was detected to be higher in saliva of HIV infected patients than in control [72]. Thus, specific kits were designed to measure the levels of these inflammatory molecules from saliva to be predictive of HIV infection. A study showed the comparison between sensitivity and specificity of samples obtained from oral fluid and serum for the evaluation of different viral Hepatitis type. It was found that samples obtained from saliva showed almost 100% sensitivity and specificity for the immunoglobin (Ig) M of Hepatitis A virus (HAV), surface antigen of Hepatitis B virus (HBV) and antibody of Hepatitis C virus (HCV), confirming that oral sampling offers opportunities for efficient prognosis [73]. In

another study based on identification of salivary transcriptome factors in oral squamous cell carcinoma (OSCC), levels of different mRNA signatures were determined. Among the different identified targets, seven genes were found to be significantly upregulated in the following order: high-*IL8*, moderate-*H3 histone family member 3A* (H3F3A), S100 Calcium Binding Protein P (*S100P*), *IL1B*, dual specificity phosphatase 1 (*DUSP1*), low-spermidine/spermine N1-acetyl transferase (*SAT*) and Ornithine decarboxylase antizyme 1 (*OAZ1*) [74]. Each of the identified gene has a role in cancer-specific pathways and is often deregulated leading to diseased progression. Therefore, the combination of identified salivary biomarkers with sensitivity and specificity of around 90% could help in early diagnosis of oral cancer and could be explored for other cancer types as well.

A study analyzed the level of protein c-ErbB-2 or HER2/neu in patient saliva with/without breast cancer [75]. The oncogenic protein is considered a prognostic marker having been identified in the tissue biopsies of patients with malignant tumor. The results showed that c-ErbB-2 level identified from saliva was upregulated and could therefore be used in the diagnosis of patients and to monitor disease recurrence. In another study based on salivary proteomics technology, protein profiles of patients with generalized aggressive periodontitis (GAgP) were compared with that of controls and 11 proteins were found to be altered [76]. Thus, salivary diagnostics identifying peptides and salivary proteins could play a significant role in understanding the cause of associated disease. In case of lung cancer, a study identified the methylation status of promoters of different TSGs in sputum of lung cancer patients. Promoters of genes such as O6-methylguanine DNA methyltransferase (MGMT), RAS association domain-containing protein 1(RASSF1A), death-associated protein kinase (DAPK) and B cell lineage-specific activator protein (PAX5a or BSAP) were highly methylated in patients who had survived lung cancer (these patients had a 6% recurrence risk) [77]. A similar study on head and neck squamous cell carcinoma (HNSCC) found promoters of similar TSGs to be hypermethylated and therefore important for the diagnosis in saliva of patients. These include RASSF1a, p16 INK4A, DAPKI and MGMT, confirming that these biomarkers play an important role and that methylation status of gene promoters is associated with increased cancer risk [78].

Other than saliva, another noninvasive accessible biomarker that can be used for disease diagnosis and prevention is urine. A study identified the methylation status of different TSGs in patients suffering from bladder cancer and found it to correlate with tumor grade. The TSGs identified were cyclin D2 (CCND2), Secretoglobin Family 3A Member 1 (SCGB3A1), BCL2 Interacting Protein 3 (BNIP3), DNA-binding protein inhibitor ID-4 (ID4) and Runt-related transcription factor 3 (RUNX3) [79]. Another study on pediatric tumors identified two biomarkers tissue inhibitor of metalloproteinases-3 (TIMP3) and basic fibroblast growth factor (bFGF) to be involved in detection of juvenile pilocytic astrocytomas (JPAs) in the brain [80]. The expression of biomarkers correlated to tumor grade and their levels decreased after treatment.

3. Overview of noncoding RNAs

Noncoding RNA (ncRNA) is RNA transcript that do not encode for the protein. In term of their sizes ncRNAs on threshold of 200 nucleotides length, are categorized in two types, small noncoding RNAs and long noncoding RNAs (lncRNAs). Small noncoding RNAs are sub categorized into microRNAs (miRNAs), small nucleolar RNAs (snoRNAs) and piwiRNAs

(piRNAs) [81]. On the basis of their location with respect to protein coding genes, lncRNAs are categorized into: intergenic lncRNAs (present between two protein coding genes), intronic lncRNAs (introns of protein coding genes transcribe them), overlapping lncRNAs (a coding gene is located on the intron), antisense lncRNAs (the opposite strand of protein coding gene transcribe them) and processed lncRNAs (lacks an open reading frame ORF) [82]. These ncRNAs play an important role in different biological processes and are often deregulated in cancer. In this section, we will discuss ncRNAs as a potential biomarker, providing rationales for the development of therapeutics targeted against or based on these ncRNAs.

3.1. miRNA

miRNAs are universally present in plants and mammals and are single-stranded RNA of 18–25 nucleotides in length. They regulate gene expression mainly at the posttranscriptional level in a sequence specific manner either by translational repression or by cleavage of their target mRNAs. Lin-4 and let-7 were identified in *C. elegans* as the first miRNAs. They were involved in nematode development. As many as 1881 precursors, 2588 mature; 495 precursors, 765 mature and 1193 precursors, 1915 mature microRNAs have been interpreted in the human, rat and mouse, respectively, till date and this collectively has been cataloged in the miRNA Registry (http://microrna.sanger.ac.uk, V 21 July, 2014) [83]. Approximately one-third of the protein coding genes are believed to be controlled by miRNAs. These are first transcribed as pri-miRNA of more than 150 nucleotide (nt) long and then the stem loop is processed by an exonuclease Drosha in the nucleus, which results in pre-miRNA of 70 nt intermediate. These duplex pre-miRNAs are then exported to cytoplasm by Exportin-5 and Ran-GTP. They are then processed by Dicer to form mature miRNA of 22–29 nucleotide in length. Then they become part of RNA induced silencing complex (RISC), where one strand is cleaved (depending on the stability of 5'end) and the other remaining one functions as mature strand. Then this strand depending on the complementarity of the target mRNAs inhibits the translational initiation. miRNAs are expressed in different cells and at different stages, thereby play a crucial role in the regulation of various biological processes in various stages. They have been involved in several diseases like cancer [84]. Urgency for early cancer diagnosis and differentiating multiple cancer types is guiding the way for identifying miRNA signatures and monitor disease.

3.1.1. Techniques for miRNA quantification

Various methods have been developed by researchers to identify miRNAs in body fluids and tumors. Northern blotting is quantitative technique, which is used to detect RNA, but lacks sensitivity [85]. Researchers have used quantitative polymerase chain reaction (q-PCR) based on stem loop primers, that can differentiate between miRNAs isomers. Like whole genome array, miRNA microarray is used to differentiate deregulated miRNAs. Recently high throughput sequencing techniques have undergone a number of developmental changes and small RNA sequencing has been used to identify the novel miRNAs.

3.1.2. Benefits of using miRNA as biomarkers

miRNAs are deregulated frequently in several diseases and are specific to the tissues but some of them are highly conserved in different species and secreted in body fluids thereby serving as potential candidates for biomarkers. In comparison to large and extensive mRNA

expression signatures and identifying unknown tumor origin, miRNA signatures have shown more predictive power.

3.2. miRNAs as biomarker in different cancers

3.2.1. Lung cancer

Lung cancer is one of the major causes of cancer-related deaths in both men and women. Lung cancer is extremely difficult to detect in its early stages and the most prevalent is NSCLC [86]. The effectiveness of NSCLC treatment is expected to be improved through the implementation of robust and specific biomarkers. Novel targeted therapies are being developed based on molecular characteristics. Junichi et al. provided the first evidence of miRNAs role in lung cancer. Let-7 is reduced in human lung cancer and this alteration may have a prognostic impact in lung cancer patients who are surgically treated [87]. Global profiling studies have been done to identify the relationship between alterations of miRNAs and patient outcome. Deregulation of miR-155 and miR-let-7a-2 correlated with poor survival. Univariate analysis as well as multivariate analysis for hsa-mir-155 predicted poor survival [88]. In another global profiling study, investigators identified a set of five microRNAs to construct a signature by the risk score method. They have shown two microRNAs (hsa-miR-221 and hsa-let-7a) to be protective, and the other group (hsa-miR-137, hsa-miR-372 and hsa-miR-182∗) to be predictive of disease progression [89]. Similar genome-wide miRNA expression in patients with NSCLC (plasma samples) was performed and a signature of 24 circulating miRNAs was identified. This study was done by profiling 754 miRNAs in 100 NSCLC patients, showing a strong and highly predictive miRNA signature [86]. Another study done in TRAIL-resistant NSCLC shows miR-221 and miR-222 expression to be elevated, which is necessary to maintain TRAIL-resistant phenotype, thus making them as potential therapeutics or diagnostic tools [90]. Gasparini et al. profiled NSCLCs and showed that the NSCLCs can be classified into as rearranged ALK, mutated EGFR or mutated KRAS versus wild type based on miR-1253, miR-504 and miR-26a-5p expression levels [91].

3.2.2. Prostate cancer

Prostate cancer accounts for almost 15% of all new cancers in men. Several studies have linked circulating miRNAs expression to serve as accurate biomarkers for prostate cancer diagnosis. Singh et al. profiled expression of miRNAs in serum of prostate cancer patients that underwent radical prostatectomy. They identified a panel of 43 miRNAs that could help in differentiation of disease stages in 14 prostate cell lines and patient samples and correlated the expression of miR-222 and miR-125b as prognostic marker in these patients [92]. Another group identified miR-205 and miR-214, which were downregulated in prostate cancer and predicted it as potential biomarker in prostate cancer [93]. Circulating miRNAs that are most deregulated in men with high risk prostate cancer, metastatic and castrate-resistant prostate cancer (CRPC) includes miR-21, miR-141 and miR-221 [94, 95]. These data suggest the diagnostic importance of less invasive biological fluids as sources of biomarkers than blood or tissue of prostate cancer.

Many miRNAs (miR-155, miR-31, miR-152 and miR-137) host genes promoters that are associated with CpG island, recent studies have shown these to be hypermethylated in prostate cancer [96]. They have shown the upregulation of KDM5B, a lysine-specific demethylase, to be associated with the methylated status of the host gene promoter of miR-137 and miR-155.

These methylated miRNAs host genes are promising diagnostic and/or prognostic biomarkers of prostate cancer. miR-193b has been implicated in prostate cancer with high sensitivity and specificity, whereas high miR-129-2 and miR-34b/c methylation levels are prognostic markers for disease-free survival [97]. Jacob Fredsøe et al. developed a novel urine-based three-miRNA prognostic model (miR-125b-5p*, let-7a-5p/miR-151a-5p) for prediction of biochemical resource after radical prostatectomy in prostate cancer [98]. miR-125b, let-7a and miR-151a inhibit apoptosis, reduce proliferation and promote cell migration and invasion of prostate cancer cells, respectively, suggesting that these miRNAs could play a functional role in prostate cancer progression [98].

3.2.3. Triple negative breast cancer

Triple negative breast cancer (TNBC) treatment is difficult and it accounts for 20% of all breast cancers in women. Researchers are developing markers to detect breast cancer at early stage, which can lead to better disease outcome and prolonged patient survival. miRNAs have been shown to play a regulatory role in cell cycle progression, apoptosis, epithelial-mesenchymal transition, angiogenesis and drug resistance in breast cancer [99]. miR-125b, miR-145, miR-21 and miR-155 were deregulated in a genome-wide miRNA expression profile study. This deregulation correlated with the expression of estrogen and progesterone receptor, stage of tumor and vascular invasion which demonstrate the existence of breast cancer-specific miRNA signatures [100]. In a recent study, researchers identified five miRNA signature (miR-92a-3p, miR-342-3p, miR-16, miR-21 and miR-199a-5p) to investigate the role of plasma miRNAs in TNBC, using a microarray platform. These five miRNA signatures are associated with increased risk of breast cancer [101]. Our group has shown miR-22 to regulate metastasis in breast cancer by downregulating TIP60, an acetyl lysine transferase and miR-22 and TIP60 levels could be used as a prognostic marker for breast cancer [102].

3.2.4. Ovarian cancer

miRNA deregulation is prominent feature in ovarian cancer, thereby playing an important role in regulation of ovarian physiology. miR-125b, miR-29b, miR-29a and let-7 are downregulated in epithelial ovarian cancers (EOC) and are highly expressed in normal ovarian tissues. Researchers in this study have linked this deregulation of miRNA during normal ovarian functioning to EOC pathogenesis. High grade serous EOC with BRCA1/2 mutations or loss have high miR-29a and miR-29b expression [103]. In tumor tissues, 39 miRNAs are significantly deregulated in comparison to normal ovary, of which miR-200a, miR-141, miR-200c and miR200b were most significantly overexpressed whereas miR-199a, miR-140, miR-145 and miR-125b1 were most downregulated [104]. Eight miRNAs (miR-25, miR-506, miR-29c, miR-182, miR-128, miR-101, miR-141 and miR-200a) that were downregulated were predicted to regulate majority of miRNA-associated genes, which suggests the importance of miRNA networks as predictors of EOC survival [105].

3.2.5. Gastric cancer

Gastric cancer (GC) is one of the deadliest cancers in the world. Presence of sensitive and specific biomarkers for early detection and monitoring the progression of GC could lead to the reduction of mortality. Chun et al. used antisense miR-221 and miR-222 in SGC7901 cells and

showed that these miRNAs regulate radio sensitivity, cell growth and invasion by directly modulating PTEN expression in these cells [106]. Their study suggested inhibiting miR-221 and miR-222 might be a novel therapeutic strategy for human GC. Another group showed miR-18a, which is a component of miR-17-92 cluster, to be overexpressed in GC tissue [107]. They found that the cell line overexpressing miR-18a showed increase in cell number and concentration of miR-18a in cultured medium, suggesting that miRNA might be released from cancer cells into the surrounding environment. They then concluded circulating miR-18a to be a useful biomarker for screening and monitoring tumor dynamics in GC [107].

Wang et al. did meta-analysis in 107 studies published in 42 articles and identified circulating miRNAs, miR-203, miR-146b-5p, miR-192 and miR-200c. They used bivariate model to calculate the sensitivity and specificity and used to plot the area under the summary receiver operator characteristic curve (AUC). The AUC is interpreted as the probability to correctly distinguish patients from normal controls. Using these parameters, they showed miR-203, miR-146b-5p, miR-192 and miR-200c has sensitivity of 0.75, a specificity of 0.81 and an AUC of 0.85, showing good diagnostic performance in gastrointestinal cancers [108]. They concluded based on this study that circulating miRNAs specially a cluster of miRNA may present as promising biomarkers for the diagnosis of GC.

3.2.6. Pancreatic cancer

In digestive system, pancreatic cancer is the most aggressive cancer and worldwide it is a serious health problem. There is lack of prognostic and diagnostic marker due to which the overall survival of pancreatic cancer is poor. To search for effective biomarker in pancreatic cancer, miRNAs have been investigated in pancreatic tumor tissue, blood samples, pancreatic juice, stool and urine [109]. The miRNAs, miR-143, miR-223 and miR-30e showed increased levels in urine of stage 1 pancreatic ductal adenocarcinoma in comparison to healthy individuals. The combinational use of miR-143 and miR30e showed a sensitivity of 83.3% and a specificity of 96.2% in PDAC [110]. Another group showed miR-21 and miR-155 upregulation in PDAC and this deregulation is detected early in intraductal papillary mucinous neoplasm (IPMN), which suggests that these miRNAs can be considered as markers of transformation [111].

Li et al. identified another miRNA, miR-1290 in the serum of PDAC patients by q-PCR using TaqMan microRNA arrays [112]. In tumor tissue, it is overexpressed and shows prognostic significance. It also showed a higher diagnostic accuracy than CA19-9 in their cohort (AUC 0.86 vs. 0.77 in the group PDAC vs. healthy controls). Another group showed five miRNAs including miR-10b, miR-155, miR-106b, miR-30c and miR-212 in plasma and bile, had excellent accuracy, sensitivity and specificity for detection of PDAC over the control [113].

3.2.7. Hepatocellular cancer

In HCC, miR-15b,miR-21, miR-130b and miR-183 showed upregulation in HCC tissue as compared to adjacent non-tumor tissue [114]. These miRNAs were detected in serum and cell culture medium but showed decreased levels after surgical resection. They also showed miR-15b and miR-130 could be used to distinguish HCC from healthy samples with high sensitivity and specificity. Kourtidis et al. showed miR-30b overexpression restores the abnormal cell growth in liver cancer cell lines. The abnormal cell growth reversed, on restoring miR-30b levels [115]. The miRNAs have been shown to have a great potential as a biomarker for HCC but

till date there is no consensus on detection or good miRNA sets, for example, there is a better response to interferon therapy on miR-26 downregulation but this is associated with poor survival [116]. A summary of miRNAs involved in different cancers is presented in **Table 1**.

3.3. Long-noncoding RNA

Long noncoding RNAs (lncRNAs) are the RNA transcript that do not encode for proteins and do not have open reading frame. lncRNAs are transcribed by RNA polymerase II and controlled by the transcriptional activators of the SWI/SNF complex. lncRNA transcripts are usually spliced, capped and polyadenylated, similar to mRNAs. lncRNAs represent a heterogeneous group of ncRNAs and they are usually expressed in tissue and cellular context, and are localized in the both nucleus and cytoplasm. The presence of secondary structures in lncRNA such as stem loops and hairpins, help them to interact with proteins and chromatin and are important for various functions of lncRNAs. In general, lncRNAs act as guides to recruit proteins, scaffolds for grouping protein complexes, transcriptional enhancers by chromatin reorganization, decoys to release proteins from chromatin or antagonists for other regulatory ncRNAs, for example, miRNAs.

3.4. lncRNAs as biomarker in cancer

3.4.1. Breast cancer

Expression levels of lncRNAs have been investigated in breast cancer tissues compared to normal tissues indicating that some may be potential biomarkers for breast cancer diagnosis. lncRNA-BC2 and lncRNA-BC5 were upregulated and lncRNA-BC4 and lncRNA-BC8 were downregulated in breast cancer patient samples in a study done by Ding et al. [117]. In grade 3 breast cancer, lncRNA-BC4 expression was significantly lower and lncRNA-BC5 expression was significantly higher. lncRNAs have been demonstrated to be easily detected in bodily fluids by multiple studies, such as lncRNA RP11-445H22.4 was found to be significantly increased in breast cancer patients serum with high sensitivity and specificity [118]. Zhao et al. identified a set of lncRNAs are deregulated in breast cancer patients and distinguish low-risk patients from high risk patients. Breast cancer patients with high expression of LINC00324 and low expression of PTPRG antisense RNA 1 (PTPRG-AS1) and small nucleolar RNA host gene 17 (SNHG17) co-related with longer overall survival and tumor grade [119]. High SPRY4 intronic transcript 1 (SPRY4-IT1) expression levels was increased in 48 breast cancer tissues in comparison to normal tissue and this upregulation was found to be associated with increased tumor size, poorer prognosis and disease-free survival (DFS) [120].

Hox transcript RNA (HOTAIR) is overexpressed in breast cancer tissue and increases the invasion and metastatic capacity. This increased expression is predictive of overall survival and progression-free survival [121, 122]. Metastasis-associated lung adenocarcinoma transcript 1's (MALAT1) is upregulated in 26 pairs of estrogen receptor positive breast cancer patients. Further analysis of a larger group of breast cancer patients comprised of 204 samples and correlated high expression of MALAT1 with ER+ breast cancer patients [123]. In an analysis of 151 breast cancer tissues, which comprised of stages 1–111 invasive ductal carcinoma, lncRNA BC040587 was found to be downregulated and this downregulation was correlated with differentiation of tumor and status of menopause [124]. LINC00472 is highly expressed

in non-metastatic breast cancer tissues and the high expression of LINC00472 was associated with Luminal A type of breast cancer. High expression of LINC00472 showed reduced risk of relapse and death in patients [125, 126]. Lei zhong et al. analyzed 600 breast cancer patients with ER^+ status from the TCGA data and identified six lncRNAs (HAGLR, STK4-AS1, DLEU7-AS1, LINC00957, LINC01614 and ITPR1-AS1) gene signature as prognostic survival biomarkers [127].

3.4.2. Ovarian cancer

Guo et al. performed genome-wide miRNA and lncRNA expression profiles and categorized ovarian cancer patients (BRCA1/2 wild-type) into high and low survival on the basis of LINC01234 and CCDC144NL-AS1 and two miRNAs (miR-637 and miR-129-5p) signatures [128]. Wang et al. identified seven lncRNAs such as XR_948297, XR_947831, XR_938728, XR_938392, NR_103801, NR_073113 and NR_036503, which were deregulated in most ovarian tumor samples and showed significant correlation with a poor chemotherapeutic response of EOC patients [129]. Rong Liu et al. identified signature lncRNAs such as ZFAS1, RP5-1061H20.5, RP11-489O18.1, RP11-136I14.5, RP11-16E12.1, CTD-2555A7.3, LINC01514 and TUG1 to play a mechanistic role in chemotherapeutic resistance in HGS-OvCa tumors and act as diagnostic markers [130].

3.4.3. Leukemia

In AML patients, lncRNAs MEG3 are poorly expressed and overexpression of MEG3 inhibits AML cells proliferation, regulates cell cycle and promotes apoptosis [131]. Diaz-Beya et al. have reported that HOTAIRM1 is highly expressed in 215 intermediate-risk AML patients and this expression is associated with poor prognosis, overall survival and disease recurrence [132]. In AML patients with Nucleophosmin 1 (NPM1) mutation, a higher expression of HOTAIRM1 is associated with poor clinical outcome. Another study by De Calra et al.

Cancer	miRNAs	Expression	Clinical features	Refs.
Breast	miR-21, miR-155	Upregulated	Plasma of patient with TNBC (n = 5) and non-TNBC (n = 5), as well as healthy controls	[100]
	miR-10b, miR-125b, miR-145, miR-21	Downregulated		
	miR-145, miR-451	Downregulated	Novel biomarkers for early detection	[183]
	let7a, miR-21,miR-141, miR-214	Upregulated		
	miR-92a-3p, miR-342-3p	Upregulated	Expression is correlated with tumor stage and subtypes	[101]
	miR-16, miR-21 and miR-199a-5p	Downregulated		
	miR-210	Upregulated	Hypoxic environment in breast cancer	[184]
	miR-451	Upregulated	Multidrug resistance in breast cancer	[185]
	miR-22	Upregulated	Epithelial-mesenchymal transition, metastasis	[102]
	miR-18a	Upregulated	Paclitaxel resistance	[186]

Cancer	miRNAs	Expression	Clinical features	Refs.
Gastric	miR-433, miR-9	Downregulated	Marker for the advanced gastric carcinoma	[187]
	miR-221, miR-222	Upregulated	Regulate radio sensitivity, and cell growth and invasion by directly modulating PTEN expression	[106]
	miR-203, miR-146b-5p, miR-192, miR-200c	Upregulated	Diagnostic marker	[108]
	miR-214, miR-17, miR-20a, miR-200c, miR-107, miR-27a, miR-433, let-7 g, miR-125a-5p, miR-760, miR-206, miR-26a	Upregulated	Poor prognosis in gastrointestinal cancer patients	[188]
	miR-200b, miR-185	Downregulated		
	miR-125a, miR-137, miR-141, miR-146a,	Downregulated	Prognostic marker	[189]
	miR-206, miR-218, miR-486-5p, miR-506			
	miR-451, miR-199a-3p, miR-195	Upregulated	Poor prognosis for recurrence and survival	[190]
	let-7 g, miR-342, miR-16, miR-1, miR-34	Upregulated	Associated with chemosensitivity	[191]
	miR-18a	Upregulated	Increase in cell number and released in cell culture medium	[107]
Hepatocellular carcinoma	miR-15b, miR-21, miR-130b, miR-183	Upregulated	High sensitivity and specificity in HCC patients	[192]
	miR-16, miR-195, miR-199a	Upregulated	HBV-associated HCC samples from healthy controls	[193]
	miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192, miR-505	Upregulated	HBV-associated HCC from chronic HBV infection	[192]
	miR-200c, miR-200, miR-21, miR-224, miR-224, miR-10b, miR-222	Upregulated	HBV-related HCC compared to patients with chronic HBV	[194]
	miR-517a, miR-520c	Upregulated	Downregulation of both miR-517a and miR-517c contribute to HCC development through Pyk2 regulation	[195]
	miR-18a, miR-224, miR-199a*, miR-195, miR-199a, miR-200a, miR-125a	Upregulated	Promotes tumor progression	[196]

Cancer	miRNAs	Expression	Clinical features	Refs.
Ovarian	miR-125b, miR-29b, miR-29a, let-7	Downregulated	Epithelial ovarian cancer pathogenesis	[103]
	miR-519a	Upregulated	Poor prognosis of patients with ovarian cancers	[197]
	miR-25, miR- 506, miR-29c, miR-182, miR-128, miR-101, miR-141, miR-200a	Downregulated	miRNA networks as predictors of epithelial ovarian cancer survival	[105]
	let-7e, miR-30c, miR-130a, miR-335	Upregulated	Prognostic tool to monitor the chemotherapy outcome	[198]
	miR- 125b	Downregulated		
	miR-214, miR-199a*, miR-200a	Upregulated	Cell survival and cisplatin resistance	[199]
	miR-100	Downregulated		
	mir-135b, miR-200a, miR-200b, miR-200c, miR-141, miR-429	Upregulated	Prognostic and diagnostic marker	[200]
	miR-205, miR-449, miR-429	Upregulated	Diagnostic marker in endometrioid ovarian cancer	[201]
	miR-204, miR-99b, miR-193b	Downregulated		
Lung	miR-155 and miR-let-7a-2, miR-145, miR-21	Upregulated	Associated with adenocarcinoma patients survival	[88]
	miR-221, miR-222	Upregulated	Induce TRAIL resistance and enhance cellular migration	[90]
	miR-1253, miR-504, miR-26a-5p	Upregulated	Therapeutic target to overcome resistance to ALK inhibitors	[91]
	miR-1343-3p miR-671-3p, miR-103a-3p	Upregulated	Deregulated in cancerous vs. normal lung tissue	[202]
	let-7e, miR-342-3p	Downregulated		
	miR-210, miR-182, miR-486-5p, miR-30a, miR-140-3p	Upregulated	Poor survival in squamous carcinoma	[203]
	miR-31	Downregulated		
	let7g, miR-26	Downregulated	Deregulated in squamous carcinoma vs. adenocarcinoma	[204]
	miR-21	Upregulated	Marker of tumor progression in adenocarcinoma	[205]

Cancer	miRNAs	Expression	Clinical features	Refs.
Pancreatic	miR-143, miR-223, miR-30e	Upregulated	Overexpressed in patients with stage I cancer when compared with age-matched healthy individuals	[110]
	miR-21, miR-155	Upregulated	Expression was significantly correlated with tumor stage and poor prognosis	[111]
	miR-20a, miR-21, miR-24, miR-25, miR-99a, miR-185, miR-191	Upregulated	Prognostic biomarker with high sensitivity and specificity	[206]
	miR-10b, miR-155, miR-106b, miR-30c, miR-212	Upregulated	Excellent accuracy, sensitivity and specificity for detection of PDAC over the control patients	[113]
Prostate	miR-222, miR-125b	Upregulated	Prognostic marker in prostate cancer patients	[92]
			Metastasis	
	miR-21, miR-221	Upregulated	Analysis of miR-21, -141, and -221 in blood of PCa patients reveals different pattern of molecules in clinical subgroups of PCa	[94, 95]
	miR-141	Downregulated		
	miR-155, miR-31, miR-152, miR-137	Upregulated	Hypermethylated	[96]
	miR-1290, miR-375	Upregulated	Decreased overall survival in Castration-resistant prostate cancer (CRPC) patients	[207]
	miR-375, miR-141	Upregulated	Released into incubation medium from androgen-stimulated cells	[208]
	miR-16, miR-92a,miR-103, miR-107,miR-197, miR-34b, miR-328, miR-485-3p, miR-486-5p, miR-92b, miR-574-3p, miR-636, miR-640, miR-766, miR-885-5p	Upregulated	Upregulated in serum from prostate cancer patients compared to normal donor sera	[209]
	miR-125b-5p*let-7a-5p/ miR-151a-5p	Upregulated	Urine-based three-miRNA prognostic model for prediction of BCR	[98]

Table 1. Summary of various miRNAs involved in different cancers, their expression and clinical features.

have recently identified XLOC_109948 long noncoding RNA as a strong prognostic factor in NPM1-mutated patients [133]. An association study performed in a case-control cohort made up of 149 leukemia patients, including Philadelphia positive (Ph(+)) acute lymphoblastic leukemia (ALL) and AML samples, and 183 healthy controls. They found a single nucleotide polymorphism mapping to CDKN2BAS encoding for ANRIL antisense noncoding RNA showed significant correlation with the ALL phenotype [134]. In neoplastic T lymphocytes samples from 21 children with ALL, T-ALL-R-lncR1 was expressed in 11 cases. T-ALL-R-lncR1 might be associated with T-ALL, provide a new entry point for early diagnosis and targeted therapy for T-ALL [135]. In 68 chronic lymphocytic leukemia (CLL) patients, 62 multiple myeloma (MM) patients and 36 healthy controls, 5 lncRNAs (Taurine upregulated gene1 (TUG1), lncRNA-p21, metastasis-associated lung adenocarcinoma transcript-1(MALAT1), HOTAIR and growth arrest-specific 5 (GAS5)) were identified, of which lncRNA-p21 showed low expression in CLL patients [136]. lncRNA-p21 forms a complex with hnRNPK ribonucleo

protein and suppresses cell cycle regulatory genes on stimulation by p53 [137]. lncRNA-p21 could be developed as a biomarker for the disease or drug design. Miller et al. showed translation regulatory long noncoding RNA 1 (TRERNA1) is overexpressed in 144 CLL patients' samples, act as enhancer and regulate expression of-SNAIL in cis-dependent manner [138]. They have also correlated the high expression of TRERNA1 with shorten treatment time. TRERNA1 expression resulted in decreased DNA damage and cell death in B-CLL cell line, suggesting TRERNA1 as a novel biomarker.

3.4.4. Lung cancer

lncRNAs have been successfully isolated from bronchial brushings, biopsies and sputum. Still only, few species of lncRNAs have been identified in biofluids; therefore, more sampling methods are required. Recently, there have been progresses in discovery of lncRNA biomarkers in lung cancer. MALAT-1 emerged as most promising candidate NSCLC in tissue specimens [139]. MALAT-1 is overexpressed and is a prognostic marker for metastasis and poor prognosis in cancer that arises from squamous cell carcinoma. In small cell lung cancer (SCLC) patients, CCAT2 was associated with shorter overall survival. High expression of CCAT2 was an independent unfavorable prognostic factor for SCLC patients as analyzed by univariate and multivariate analyses [140]. Qiu et al. showed CCAT2 is upregulated in NSCLC tissues in comparison with paired adjacent normal lung tissues and this overexpression is significant in lung adenocarcinoma but not in squamous cell carcinoma [141].

Zhang eb et al. have shown that the lncRNA TUG1 was downregulated in lung cancer tissues and this correlates with advanced pathological stage, greater tumor size and shorter survival time in both lung squamous cell carcinoma and lung adenocarcinoma [142]. Sun et al. have demonstrated that the downregulation of SPRY4-IT1 correlated with larger tumor size, advanced pathological stage and lymph node metastasis in NSCLC patients and this reduced expression of SPRY4-IT1 with lymph node metastasis status may serve as a biomarker of late stage and poor survival [143].

3.4.5. Prostate cancer

Recently, a lot of progress has been made in identifying the lncRNAs as biomarker in prostate cancer and the most recent one is the PCA-3 assay, which has been approved by the FDA. In prostate cancer, PCA3 was suggested as a urinary biomarker and detected using q-PCR in a cohort of 108 men [144]. One of the lncRNA extensively studied in prostate cancer pathogenesis is prostate cancer-associated intergenic noncoding RNA transcript 1 (PCAT1). In 102 prostate cancer tissues, PCAT1 was upregulated and correlated with disease progression [145]. Srikantan et al. found prostate cancer gene expression marker 1 (PCGEM1) to be upregulated in African-American men compared to Caucasian-American men and is associated to patients with high prostate cancer risk [146].

Schlap1 showed higher expression in metastatic prostate cancer and the expression of Schlap1 correlated with metastasis and prostate cancer-specific mortality [147–149]. Another study did RNA sequencing and found prostate cancer-associated noncoding RNA transcript 18 (PCAT-18) to be upregulated in prostate cancer in comparison to neoplasm. In prostate cancer cell lines, PCAT-18 inhibits cell invasion, migration and proliferation, which suggest it to be a therapeutic target and biomarker for prostate cancer [150]. Isin et al. analyzed exosomes from

the urinary samples from 30 prostate cancer patients and 49 benign prostatic hyperplasia (BPH) patients and found lncRNA-p21 to be deregulated, whereas another lncRNA GAS5 expression was not changed [151]. This result suggested lncRNA-p21 as a biomarker for the prostate cancer detection. Ren et al. has demonstrated lncRNA FR0348383 to be differentially expressed and its expression levels could differentiate prostate cancer from BPH. Another group has reported same lncRNA as a novel biomarker in prostate cancer detection using post-digital rectal examination (post-DRE) urine of the patients [152].

3.4.6. Liver cancer

The lncRNA urothelial carcinoma-associated 1 (UCA1) is shown as a single lncRNA-based HCC diagnostic approach. In both studies, UCA1 performed better than Alpha-fetoprotein (AFP). In combination with JUN mRNA, UCA1 lncRNA showed 90% sensitivity and 80% specificity and in early stage HCC detection, the same combination showed 100% sensitivity and 80% specificity underlining the importance of RNA-based detection methods for early stage HCC diagnosis [153]. In 86 (35 female, 51 male) HCC patients, Liu et al. showed NEAT1 to be overexpressed in HCC patients and this was an independent risk factor associated with the prognosis of patients [154]. Wang et al. analyzed TCGA data and shown the expression profiles of four lncRNAs (RP11-322E11.5, RP11-150O12.3, AC093609.1 and CTC-297N7.9) for 371 patients with HCC were significantly and independently associated with survival of HCC patients [155]. Several studies suggested circulating ncRNAs and tumor tissue-derived ncRNAs for HCC diagnosis or survival prediction [156, 157]. While tissue-derived ncRNAs might be functionally relevant in the tumor, they are not necessarily good biomarkers for diagnosis. To obtain a tissue sample, a liver biopsy is needed, which is an invasive procedure with potential side effects. Therefore, the detection of circulating ncRNAs in body fluids instead of tumor tissue is advantageous for HCC diagnosis and surveillance. A summary of lncRNAs involved in different cancers is presented in **Table 2**.

3.5. Circular RNA

Circular RNA (circRNA) is a class of RNA that are abundant, evolutionary conserved and stable. They were identified 30 years ago as a result of an error in RNA splicing, but their function in different cellular processes is now being appreciated [158]. In acute lymphoblastic leukemia (ALL) patients and cell lines, Salzman et al. discovered circRNAs by RNA sequencing [159]. After this discovery, many other circRNAs were identified, shown to be endogenously expressed as well as stable. Backsplicing of exons, introns or both results in the formation of exonic or intronic circRNAs [160]. RNA binding proteins act as activators or inhibitors in circRNA formation [39]. Conn et al. have shown that the RNA binding protein QK1 binds to the introns flanking a circRNA and forms a looped structure by dimerization promoting circularization [39]. circRNAs have been classified as noncoding RNA, but recently there have been reports suggesting that they may be translated to protein if there is a presence of internal ribosome entry site (IRES) [161–163]. Recently, circRNAs have been studied extensively in relation to human diseases, especially cancers. Here we will discuss the potential of circRNAs as potential biomarkers and as therapeutic targets. A summary of circRNAs involved in different cancers is presented in **Figure 2**.

3.5.1. Gastric cancer

Lai et al. examined co-expression networks between circRNAs and mRNAs and found three candidate (circRNA0047905, circRNA0138960 and circRNA7690-15) oncogenes in gastric tissue. circRNA0047905 was predicted as biomarker in gastric tissue as it showed highest diagnostic accuracy [164]. Huang et al. analyzed plasma samples from patients with GC and healthy controls and showed hsa_circ_0000745 to be downregulated in GC tissue. Its expression correlated with tumor formation in gastric tissue, whereas in plasma, it correlated with tumor node metastasis (TNM) stage. Expression level of hsa_circ_0000745 in plasma in combination with carcinoembryonic antigen (CEA) level is a promising diagnostic marker for GC [165]. In plasma and GC tissues, hsa_circ_002059 was shown to be upregulated in comparison to adjacent normal tissues and this deregulation was associated with metastasis, TNM, gender and age. This suggests hsa_circ_002059 as a potential stable biomarker for the diagnosis of gastric carcinoma [166]. Another study showed upregulation of circPVT1 in GC tissue due to the amplification of its genomic locus. circPVT1 acts as a sponge for miR-125 family, promotes cell proliferation and also acts as a prognostic marker for disease-free survival and overall survival of GC patient [167].

Cancer	lncRNAs	Expression	Clinical features	Refs.
Breast	lncRNA-BC2 and lncRNA-BC5	Upregulated	Positively correlated with patients' age, clinical stage, progesterone receptor (PR) concentration	[117]
	lncRNA-BC4 and lincRNA-BC8	Downregulated	Negatively correlated with PR concentration	
	LINC00324	Upregulated	Expression pattern is associated with ER+ and ER- subtypes, tumor histology	[119]
	PTPRG-AS1, SNHG17	Downregulated		
	SPRY4-IT1	Upregulated	Prognostic biomarker and therapeutic candidate for breast cancer. Biomarker for overall survival and progression-free survival	[120]
	HOTAIR	Upregulated	Potential tumor marker for breast cancer diagnosis	[121, 127]
	MALAT1	Upregulated	Poor prognosis and correlated with tumor differentiation	[123]
	BC040587, neuroblastoma-associated transcript 1 (NBAT1) and eosinophil granule ontogeny transcript (EGOT)	Downregulated	New marker of prognosis in breast cancer	[124]
	LINC00472	Upregulated	Prognostic and predictive value in the clinical management of breast cancer	[125, 126]
	HAGLR, STK4-AS1, DLEU7-AS1, LINC00957, LINC01614 and ITPR1-AS1	Upregulated	Prognostic biomarker of survival of breast cancer patients	[127]

Cancer	lncRNAs	Expression	Clinical features	Refs.
Ovarian	LINC01234 and CCDC144NL-AS1	Upregulated	Overexpression is correlated with overall shorter survival	[128]
	XR_948297, XR_947831, XR_938728, XR_938392, NR_103801, NR_073113 and NR_036503	Upregulated	Correlated with a poor chemotherapeutic response of EOC patients	[129]
	ZFAS1, RP5-1061H20.5, RP11-489O18.1, RP11-136I14.5, RP11-16E12.1, CTD-2555A7.3, LINC01514 and TUG1	Upregulated	Play a mechanistic role in chemotherapeutic resistance in HGS-OvCa tumors	[130]
Leukemia	MEG3	Downregulated	Regulate cell cycle and promote apoptosis	[131]
	HOTAIRM1	Upregulated	Associated with poor prognosis, shorter overall survival and disease recurrence	[132]
	XLOC_109948	Downregulated	Strong prognostic factor in NPM1 mutated patients	[133]
	ANRIL	Upregulated	Significant correlation with the ALL phenotype	[134]
	T-ALL-R-lncR1	Upregulated	Early diagnosis and targeted therapy of T-ALL suppress cell cycle regulatory genes	[135]
	TRERNA1	Upregulated	Decreased DNA Damage and cell death in B-CLL cell line	[138]
Lung	MALAT-1	Upregulated	Predictive marker for metastasis development and poor prognosis in cancer arising from squamous cell carcinoma	[139]
	CCAT2	Upregulated	Promotes invasion of non-small cell lung cancer	[140, 141]
	TUG1	Downregulated	Correlated with advanced pathological stage, greater tumor size and shorter survival time in both lung squamous cell carcinoma and lung adenocarcinoma	[142]
	SPRY4-IT1	Downregulated	Correlated with larger tumor size, advanced pathological stage and lymph Node metastasis in NSCLC patients	[143]

Cancer	lncRNAs	Expression	Clinical features	Refs.
Prostate	PCA3	Upregulated	Urinary biomarker	[144]
	PCAT1	Upregulated	Implicated in prostate cancer progression	[145]
	PCGEM1	Upregulated	Associated to patients with high prostate cancer risk	[146]
	Schlap1	Upregulated	Prognostic biomarker	[147–149, 210]
	PCAT-18	Upregulated	Inhibits cell invasion, migration and proliferation	[150]
	lncRNA-p21	Downregulated	Biomarker for the prostate cancer detection	[151]
	FR0348383	Upregulated	Novel biomarker in prostate cancer detection using post-DRE urine of the patients	[152]
Liver	UCA1	Upregulated	90% sensitivity and 80% specificity in early stage HCC detection	[153]
	NEAT1	Upregulated	Associated with the prognosis of patients with HCC	[154]
	RP11-322E11.5, RP11-150O12.3, AC093609.1, CTC-297 N7.9	Downregulated	Associated with prognosis of liver cancer, and could provide novel insights into the potential mechanisms of HCC progression	[155]
	HULC and Linc00152	Upregulated	Applied as a potential target for HCC treatment	[157]

Table 2. Summary of various lncRNAs involved in different cancers, their expression and clinical features.

3.5.2. Hepatocellular carcinoma

hsa_circ_0001649 expression is significantly downregulated in 89 HCC samples in comparison to adjacent liver tissue and this correlates with tumor embolus and size, indicating its use as a potential biomarker for HCC [168]. Fu et al. showed lower expression of hsa_circ_0004018 is correlated with serum AFP level, tumor diameters, differentiation, Barcelona Clinic Liver Cancer stage and TNM in HCC [169]. Using a circRNA microarray, Huang et al. identified 226 differentially expressed circRNAs, of which 189 were significantly upregulated and 37 were downregulated. circRNA_100,338, one of the upregulated circRNAs in HCC, is correlated with a low cumulative survival rate and metastatic progression in HCC patients with Hepatitis B [170]. Shang et al. performed circRNA microarray and found circ_0000520, circ_0005075 and circ_0066444 are deregulated in HCC. They found upregulation of only circ_0005075 to be associated with tumor size [171].

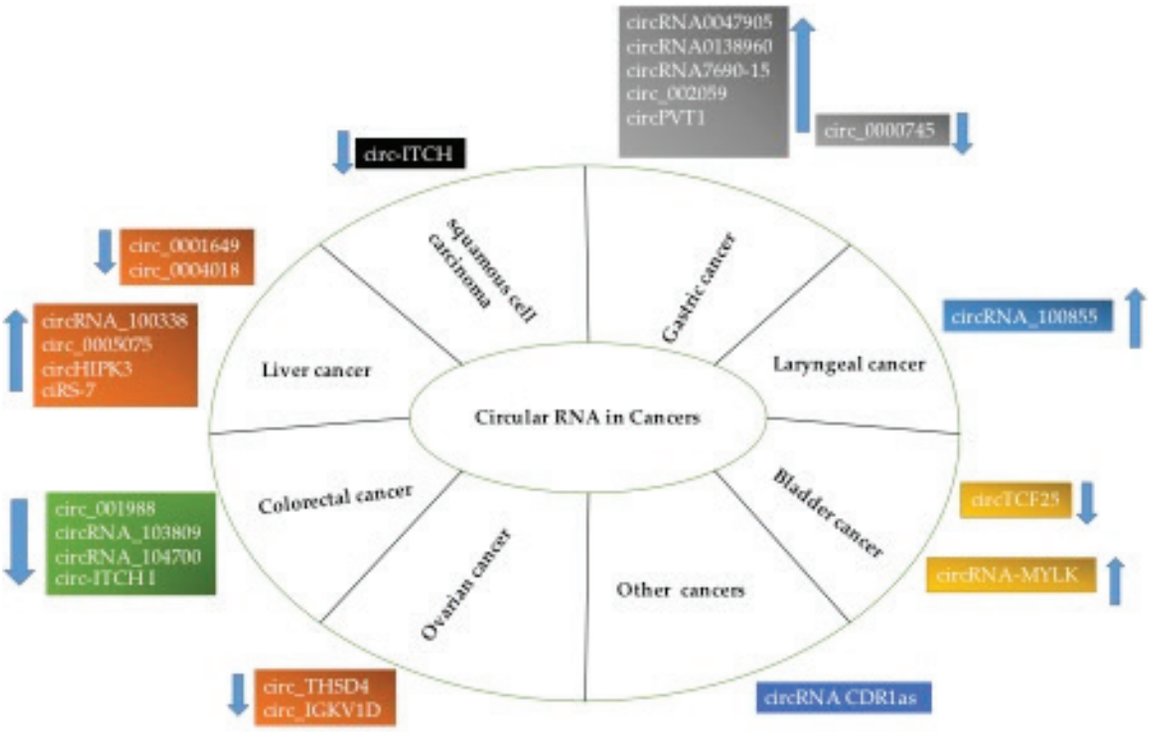

Figure 2. Circular RNAs in cancer. A list of the important circRNAs involved in different cancer types and their associated levels.

3.5.3. Colorectal cancer

In CRC, Wang et al. showed the expression of hsa_circ_001988 was decreased in tumor tissues and the expression was correlated with differentiation and perineural invasion, suggesting hsa_circ_001988 as a novel treatment target and a potential biomarker of CRC [172]. Zhang et al. performed circRNA array in paired tumor and adjacent non-tumorous tissues from six CRC patients and found lower expression of hsa_circRNA_103809 and hsa_circRNA_104700 in CRC tissues. The expression of hsa_circRNA_103809 was correlated with lymph node metastasis and tumor node metastasis stage, whereas expression level of hsa_circRNA_104700 was significantly correlated with distal metastasis. hsa_circRNA_103809 and hsa_circRNA_104700 are involved in the development of colorectal cancer and serve as potential biomarkers for the diagnosis of colorectal cancer. Another circRNA, cir-ITCH was downregulated in CRC and inhibits Wnt/β-catenin pathway by increasing ITCH expression suggesting a mechanistic role for circ-ITCH in CRC by regulating the Wnt/β-catenin pathway [173]. Studies cited above illustrate that circRNAs are promising biomarkers for CRC.

3.5.4. Laryngeal cancer

Till date not much study on circRNA profiling in laryngeal cancer have been done. Microarray analysis in four paired laryngeal squamous cell cancer (LSCC) tissues revealed 698 circRNAs to be altered. hsa_circRNA_100855 was most upregulated in LSCC when compared to adjacent non-neoplastic tissues [174]. This expression of hsa_circRNA_100855 correlated with tumor

grade, tumor stage, neck nodal metastasis and primary location of LSCC. CircRNA_100855 plays an important role in the tumorigenesis of LSCC can be used as a prognostic and diagnostic biomarkers in LSCC.

3.5.5. Bladder cancer

In bladder carcinoma, circRNA expression was done using microarray assay by Zhong et al. and researchers demonstrated that circTCF25 is overexpressed in bladder cancer and this overexpression downregulate miR-103a-3p and miR-107, increase cyclin-dependent kinase 6 (CDK6) expression and promote proliferation and migration *in vitro* and *in vivo* [175]. The data also suggested that circTCF25 might be a new biomarker for bladder cancer. In another study by the same group, they found that circRNA-MYLK and VEGFA were significantly upregulated and co-expressed in bladder cancer [176]. The expression of circRNA-MYLK co-related with the progression of stage and grade of bladder cancer, suggesting that circRNA-MYLK would be a promising target for bladder diagnosis and therapy.

3.5.6. circRNAs in other cancers

In cutaneous squamous cell carcinoma (cSCC), 322 circRNAs were identified to be deregulated and having 1603 miRNA response elements (MREs) [177]. These deregulated circRNA were shown to be involved in tumor formation by acting as a sponge for miRNAs. Another study identified circRNA expression signatures in PDAC by microarray platform [178]. They have shown that initiation and progression of PDAC is controlled by circRNAs. Li et al. found that circ-ITCH expression is downregulated in esophageal squamous cell carcinoma (ESCC) compared to the peritumoral tissue. circ-ITCH act as a sponge for miR-7, miR-17 and miR-214, thereby increasing the level of ITCH and promoting ubiquitination and degradation of phosphorylated Dvl2, thereby inhibiting the Wnt/β-catenin pathway [179]. circRNA CDR1as have 70 selectively conserved target sites of miR-7, and lot of studies have shown that miR-7 can directly downregulate oncogenes [180]. This miRNA regulation by CDR1as has been shown to be involved in cancers such as breast cancer, melanoma, GC, gliocytoma, liver cancer and NSCLC.

3.6. Noncoding therapeutics in clinical trials

To date, the use of miRNA-based therapeutics in malignant disease is poorly explored. Presently, many companies are developing miRNA as therapeutic targets either by overexpressing tumor suppressor miRNA or by inhibiting oncogenic miRNAs. miR-122 has been shown to play an important role in HCC. Currently Santaris pharma has used locked nucleic acid-based antisense oligonucleotide against miR-122, thereby reducing the miR-122 levels and playing a positive role in the regulation of Hepatitis C viral replication [181]. This antisense has already passed Phase II clinical trials and shows promising results in patients infected with HCV infection [182]. Mirna therapeutic has also developed a miR-34a mimic, for miR-34a overexpression and currently is under trials for primary liver cancer. They have also developed anti-miR-155, which has shown a promising result in restoring normal function

and reducing cell proliferation in hematological malignancies. Similarly, miR-34 liposomes are also under stage I clinical trial. Regulus therapeutics has introduced several anti-miR in preclinical trials, for example, in renal fibrosis the expression of miR-21 is high and anti-miR-21 reduces the expression of extracellular matrix proteins. In atheroclosis, anti-miR-33 has been used successfully to regulate cholesterol and fatty acid homeostasis by decreasing LDL triglycerides and increasing HDL. This anti-miR-33 has cleared the preclinical trials. In HCC, anti-miR-221 has been successful in delaying the tumor progression, thereby increasing the survival rate. miRagen therapeutics have also developed anti-miR-92 (for peripheral artery disease) and anti-miR-15 (for myocardial infarction), which are in preclinical trials.

Besides the above examples of successful trials, there are still major obstacles that need to overcome for miRNA-based therapeutics. miRNAs have multiple targets, hence the off target effects need to be examined carefully. Similarly one gene can be regulated by multiple miRNAs that can compromise the effect of miRNA-based treatment. In addition, delivery mechanism for miRNA that show high specificity and efficacy is lacking. Overall, miRNA-based therapeutics hold a promising future for personalized medicine based on miRNA biomarkers but for this, a first step towards better understanding of miRNA biology is required.

4. Conclusion

Recent advancement in techniques and the vast repertoire of information has made it feasible to identify and characterize different biomarkers. However, due to the constant evolving epigenetic landscape of cancer cells along with the heterogeneity in the cell population subtype, their translation into clinical stage offers various limitations. Additionally, population size used in the study as well as tumor samples used to identify the genes and pathways involved needs to be further validated. Samples handling methods need to be specified as variation might occur depending on the site of isolation as well as the method used to identify the specific biomarker type. Therefore, extensive research on various biomarker profiles is important to understand their potential as therapeutic and diagnostic tools in different cancer types. Integration of biomarker discovery with other techniques such as imaging (labeling) of the specified tumor target site can provide information about the disease end point and offer a noninvasive way to monitor dose requirement.

The use of advance sequencing technologies and bioinformatics approaches in studying the transcriptome of cancer has led to the identification of ncRNAs such as miRNAs, lncRNAs and circRNAs. These ncRNAs are deregulated in most of the cancers in comparison to the normal tissue, which suggests that they might play an important role in biological function of these cancers. miRNAs are the most extensively studied ncRNAs, but their potential as effective biomarkers is still in its nascent stage. A number of studies have been done to demonstrate the potential of miRNAs as biomarkers and as diagnostic tools, but challenges still remain. For example, a large dataset has to be used to successfully predict specfic miRNAs as biomarker for prognostic and diagnostics use. To ensure the accuracy of the diagnosis based on miRNAs, one has to identify all the targets of miRNAs, thus removing the false positive targets. New delivery mechanisms also need to be developed for specificity and efficacy. Similarly, the identification of lncRNAs as important regulators of cancers has potentiated their use as

promising tool for biomarkers. lncRNAs are stable in body fluids and their expression is specific to different pathological conditions. However, their development as biomarkers is still in its preliminary stage, proper normalization control and a large cohort has to be used to make the study reliable. Additionally, identification of new mutations, deletions and amplifications in the ncRNAs as well as genomic alterations affect their structure and function. circRNAs are known to be deregulated in cancers and although several studies have documented their role, many questions regarding their biogenesis and function is still unclear.

To summarize, this chapter highlights the different types of biomarkers that have been characterized in different cancer types thus far, their mode of action and their targeting strategies. The therapeutic potential of different biomarkers and their use in clinical trials has also been discussed. Despite the recent advancements, a comprehensive approach on biomarker biogenesis is required to integrate the available information and to translate them as tools of prognostic and diagnostic potential.

Author details

Shainan Hora[1,2†], Amit Kumar Pandey[1,3†] and Sudhakar Jha[1,2*]

*Address all correspondence to: csisjha@nus.edu.sg

1 Cancer Science Institute of Singapore, National University of Singapore, Singapore

2 Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

3 Amity Institute of Biotechnology (AIB), Amity University Gurgaon, Gurgaon, India

† Equal contribution.

References

[1] Ewing B, Green P. Analysis of expressed sequence tags indicates 35,000 human genes. Nature Genetics. 2000;**25**(2):232-234

[2] Wright FA, Lemon WJ, Zhao WD, Sears R, Zhuo D, Wang JP, et al. A draft annotation and overview of the human genome. Genome Biology. 2001;**2**(7):RESEARCH0025

[3] Henry NL, Hayes DF. Cancer biomarkers. Molecular Oncology. 2012;**6**(2):140-146

[4] Allegra CJ, Jessup JM, Somerfield MR, Hamilton SR, Hammond EH, Hayes DF, et al. American Society of Clinical Oncology provisional clinical opinion: Testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. Journal of Clinical Oncology. 2009;**27**(12):2091-2096

[5] Goossens N, Nakagawa S, Sun X, Hoshida Y. Cancer biomarker discovery and validation. Translational Cancer Research. 2015;**4**(3):256-269

[6] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. The New England Journal of Medicine. 2001;**344**(11):783-792

[7] Lin K, Lipsitz R, Miller T, Janakiraman S. Force USPST. Benefits and harms of prostate-specific antigen screening for prostate cancer: An evidence update for the U.S. preventive services task force. Annals of Internal Medicine. 2008;**149**(3):192-199

[8] van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, et al. A gene-expression signature as a predictor of survival in breast cancer. The New England Journal of Medicine. 2002;**347**(25):1999-2009

[9] Raposo G, Stoorvogel W. Extracellular vesicles: Exosomes, microvesicles, and friends. The Journal of Cell Biology. 2013;**200**(4):373-383

[10] van Doormaal FF, Kleinjan A, Di Nisio M, Buller HR, Nieuwland R. Cell-derived microvesicles and cancer. The Netherlands Journal of Medicine. 2009;**67**(7):266-273

[11] Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nature Cell Biology. 2007;**9**(6):654-659

[12] Peinado H, Aleckovic M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, et al. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nature Medicine. 2012;**18**(6):883-891

[13] Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. Gynecologic Oncology. 2008;**110**(1):13-21

[14] Ciravolo V, Huber V, Ghedini GC, Venturelli E, Bianchi F, Campiglio M, et al. Potential role of HER2-overexpressing exosomes in countering trastuzumab-based therapy. Journal of Cellular Physiology. 2012;**227**(2):658-667

[15] Sadovska L, Santos CB, Kalnina Z, Line A. Biodistribution, uptake and effects caused by cancer-derived extracellular vesicles. Journal of Circulating Biomarkers. 2015;**4**:2

[16] Wendler F, Favicchio R, Simon T, Alifrangis C, Stebbing J, Giamas G. Extracellular vesicles swarm the cancer microenvironment: From tumor-stroma communication to drug intervention. Oncogene. 2017;**36**(7):877-884

[17] Ha D, Yang N, Nadithe V. Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: Current perspectives and future challenges. Acta Pharmaceutica Sinica B. 2016;**6**(4):287-296

[18] Soung YH, Ford S, Zhang V, Chung J. Exosomes in cancer diagnostics. Cancers (Basel). 2017;**9**(1):8

[19] Rak J. Extracellular vesicles – Biomarkers and effectors of the cellular interactome in cancer. Frontiers in Pharmacology. 2013;**4**:21

[20] Thery C, Amigorena S, Raposo G, Clayton A. Isolation and characterization of exosomes from cell culture supernatants and biological fluids. Current Protocols in Cell Biology. 2006;**30**(1):3.22.1-3.22.29

[21] Lima LG, Leal AC, Vargas G, Porto-Carreiro I, Monteiro RQ. Intercellular transfer of tissue factor via the uptake of tumor-derived microvesicles. Thrombosis Research. 2013;**132**(4):450-456

[22] Chow A, Zhou W, Liu L, Fong MY, Champer J, Van Haute D, et al. Macrophage immunomodulation by breast cancer-derived exosomes requires Toll-like receptor 2-mediated activation of NF-kappaB. Scientific Reports. 2014;**4**:5750

[23] Tominaga N, Kosaka N, Ono M, Katsuda T, Yoshioka Y, Tamura K, et al. Brain metastatic cancer cells release microRNA-181c-containing extracellular vesicles capable of destructing blood-brain barrier. Nature Communications. 2015;**6**:6716

[24] Fang D, Kute T, Setaluri V. Regulation of tyrosinase-related protein-2 (TYRP2) in human melanocytes: Relationship to growth and morphology. Pigment Cell Research. 2001;**14**(2):132-139

[25] Ratajczak J, Miekus K, Kucia M, Zhang J, Reca R, Dvorak P, et al. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: Evidence for horizontal transfer of mRNA and protein delivery. Leukemia. 2006;**20**(5):847-856

[26] Zoller M. CD44: Can a cancer-initiating cell profit from an abundantly expressed molecule? Nature Reviews. Cancer. 2011;**11**(4):254-267

[27] Trusolino L, Bertotti A, Comoglio PM. MET signalling: Principles and functions in development, organ regeneration and cancer. Nature Reviews. Molecular Cell Biology. 2010;**11**(12):834-848

[28] Stella GM, Benvenuti S, Comoglio PM. Targeting the MET oncogene in cancer and metastases. Expert Opinion on Investigational Drugs. 2010;**19**(11):1381-1394

[29] He M, Qin H, Poon TC, Sze SC, Ding X, Co NN, et al. Hepatocellular carcinoma-derived exosomes promote motility of immortalized hepatocyte through transfer of oncogenic proteins and RNAs. Carcinogenesis. 2015;**36**(9):1008-1018

[30] Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nature Reviews. Molecular Cell Biology. 2003;**4**(12):915-925

[31] Kaposi-Novak P, Lee JS, Gomez-Quiroz L, Coulouarn C, Factor VM, Thorgeirsson SS. Met-regulated expression signature defines a subset of human hepatocellular carcinomas with poor prognosis and aggressive phenotype. The Journal of Clinical Investigation. 2006;**116**(6):1582-1595

[32] Lambrecht J, Jan Poortmans P, Verhulst S, Reynaert H, Mannaerts I, van Grunsven LA. Circulating ECV-associated miRNAs as potential clinical biomarkers in early stage HBV and HCV induced liver fibrosis. Frontiers in Pharmacology. 2017;**8**:56

[33] Liu Y, Gu Y, Han Y, Zhang Q, Jiang Z, Zhang X, et al. Tumor exosomal RNAs promote lung pre-metastatic niche formation by activating alveolar epithelial TLR3 to recruit neutrophils. Cancer Cell. 2016;**30**(2):243-256

[34] Zhu W, Jiang C, Xu J, Geng M, Wu X, Sun J, et al. Pristane primed rat T cells enhance TLR3 expression of fibroblast-like synoviocytes via TNF-alpha initiated p38 MAPK and NF-kappaB pathways. Clinical Immunology. 2015;**156**(2):141-153

[35] Li Y, Zheng Q, Bao C, Li S, Guo W, Zhao J, et al. Circular RNA is enriched and stable in exosomes: A promising biomarker for cancer diagnosis. Cell Research. 2015;**25**(8):981-984

[36] Dou Y, Cha DJ, Franklin JL, Higginbotham JN, Jeppesen DK, Weaver AM, et al. Circular RNAs are down-regulated in KRAS mutant colon cancer cells and can be transferred to exosomes. Scientific Reports. 2016;**6**:37982

[37] Tsuchida N, Ryder T, Ohtsubo E. Nucleotide sequence of the oncogene encoding the p21 transforming protein of Kirsten murine sarcoma virus. Science. 1982;**217**(4563):937-939

[38] Ivanov A, Memczak S, Wyler E, Torti F, Porath HT, Orejuela MR, et al. Analysis of intron sequences reveals hallmarks of circular RNA biogenesis in animals. Cell Reports. 2015;**10**(2):170-177

[39] Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, et al. The RNA binding protein quaking regulates formation of circRNAs. Cell. 2015;**160**(6):1125-1134

[40] Thakur BK, Zhang H, Becker A, Matei I, Huang Y, Costa-Silva B, et al. Double-stranded DNA in exosomes: A novel biomarker in cancer detection. Cell Research. 2014;**24**(6):766-769

[41] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. The New England Journal of Medicine. 2004;**350**(21):2129-2139

[42] Balaj L, Lessard R, Dai L, Cho YJ, Pomeroy SL, Breakefield XO, et al. Tumour microvesicles contain retrotransposon elements and amplified oncogene sequences. Nature Communications. 2011;**2**:180

[43] Ahn K, Kim HS. Structural and quantitative expression analyses of HERV gene family in human tissues. Molecules and Cells. 2009;**28**(2):99-103

[44] Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses, Clinical Microbiology Reviews. 2009;**22**(2):240-273 (Table of Contents)

[45] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006;**124**(4):783-801

[46] Akira S, Takeda K. Toll-like receptor signalling. Nature Reviews. Immunology. 2004;**4**(7):499-511

[47] Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochimica et Biophysica Acta. 2014;**1843**(11):2563-2582

[48] Zhou X, Fragala MS, McElhaney JE, Kuchel GA. Conceptual and methodological issues relevant to cytokine and inflammatory marker measurements in clinical research. Current Opinion in Clinical Nutrition and Metabolic Care. 2010;**13**(5):541-547

[49] Kleiner G, Marcuzzi A, Zanin V, Monasta L, Zauli G. Cytokine levels in the serum of healthy subjects. Mediators of Inflammation. 2013;**2013**:434010

[50] Araki S, Omori Y, Lyn D, Singh RK, Meinbach DM, Sandman Y, et al. Interleukin-8 is a molecular determinant of androgen independence and progression in prostate cancer. Cancer Research. 2007;**67**(14):6854-6862

[51] Benoy IH, Salgado R, Van Dam P, Geboers K, Van Marck E, Scharpe S, et al. Increased serum interleukin-8 in patients with early and metastatic breast cancer correlates with early dissemination and survival. Clinical Cancer Research. 2004;**10**(21):7157-7162

[52] Wu K, Katiyar S, Li A, Liu M, Ju X, Popov VM, et al. Dachshund inhibits oncogene-induced breast cancer cellular migration and invasion through suppression of interleukin-8. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(19):6924-6929

[53] Mardon G, Solomon NM, Rubin GM. Dachshund encodes a nuclear protein required for normal eye and leg development in Drosophila. Development. 1994;**120**(12):3473-3486

[54] Wu K, Li A, Rao M, Liu M, Dailey V, Yang Y, et al. DACH1 is a cell fate determination factor that inhibits cyclin D1 and breast tumor growth. Molecular and Cellular Biology. 2006;**26**(19):7116-7129

[55] Singh RK, Lokeshwar BL. The IL-8-regulated chemokine receptor CXCR7 stimulates EGFR signaling to promote prostate cancer growth. Cancer Research. 2011;**71**(9):3268-3277

[56] Pine SR, Mechanic LE, Enewold L, Chaturvedi AK, Katki HA, Zheng YL, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. Journal of the National Cancer Institute. 2011;**103**(14):1112-1122

[57] Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007;**128**(4):683-692

[58] De Larco JE, Wuertz BR, Yee D, Rickert BL, Furcht LT. Atypical methylation of the interleukin-8 gene correlates strongly with the metastatic potential of breast carcinoma cells. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(24):13988-13993

[59] Dimberg J, Strom K, Lofgren S, Zar N, Lindh M, Matussek A. DNA promoter methylation status and protein expression of interleukin-8 in human colorectal adenocarcinomas. International Journal of Colorectal Disease. 2012;**27**(6):709-714

[60] Liu Q, Li A, Tian Y, Wu JD, Liu Y, Li T, et al. The CXCL8-CXCR1/2 pathways in cancer. Cytokine & Growth Factor Reviews. 2016;**31**:61-71

[61] Mian BM, Dinney CP, Bermejo CE, Sweeney P, Tellez C, Yang XD, et al. Fully human anti-interleukin 8 antibody inhibits tumor growth in orthotopic bladder cancer xenografts via down-regulation of matrix metalloproteases and nuclear factor-kappaB. Clinical Cancer Research. 2003;**9**(8):3167-3175

[62] Huang S, Mills L, Mian B, Tellez C, McCarty M, Yang XD, et al. Fully humanized neutralizing antibodies to interleukin-8 (ABX-IL8) inhibit angiogenesis, tumor growth, and metastasis of human melanoma. The American Journal of Pathology. 2002;**161**(1):125-134

[63] Weaver BA. How Taxol/paclitaxel kills cancer cells. Molecular Biology of the Cell. 2014; **25**(18):2677-2681

[64] Olsen RS, Nijm J, Andersson RE, Dimberg J, Wagsater D. Circulating inflammatory factors associated with worse long-term prognosis in colorectal cancer. World Journal of Gastroenterology. 2017;**23**(34):6212-6219

[65] Islam M, Mohamed EH, Esa E, Kamaluddin NR, Zain SM, Yusoff YM, et al. Circulating cytokines and small molecules follow distinct expression patterns in acute myeloid leukaemia. British Journal of Cancer. 2017;**117**(10):1551-1556

[66] Lue H, Thiele M, Franz J, Dahl E, Speckgens S, Leng L, et al. Macrophage migration inhibitory factor (MIF) promotes cell survival by activation of the Akt pathway and role for CSN5/JAB1 in the control of autocrine MIF activity. Oncogene. 2007;**26**(35):5046-5059

[67] Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. European Journal of Surgical Oncology. 2007;**33**(3):266-270

[68] Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**(21):11514-11519

[69] Koopmann J, Rosenzweig CN, Zhang Z, Canto MI, Brown DA, Hunter M, et al. Serum markers in patients with resectable pancreatic adenocarcinoma: Macrophage inhibitory cytokine 1 versus CA19-9. Clinical Cancer Research. 2006;**12**(2):442-446

[70] Wang X, Li Y, Tian H, Qi J, Li M, Fu C, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. BMC Cancer. 2014;**14**:578

[71] Blum DL, Koyama T, M'Koma AE, Iturregui JM, Martinez-Ferrer M, Uwamariya C, et al. Chemokine markers predict biochemical recurrence of prostate cancer following prostatectomy. Clinical Cancer Research. 2008;**14**(23):7790-7797

[72] Nishanian P, Aziz N, Chung J, Detels R, Fahey JL. Oral fluids as an alternative to serum for measurement of markers of immune activation. Clinical and Diagnostic Laboratory Immunology. 1998;**5**(4):507-512

[73] Thieme T, Yoshihara P, Piacentini S, Beller M. Clinical evaluation of oral fluid samples for diagnosis of viral hepatitis. Journal of Clinical Microbiology. 1992;**30**(5):1076-1079

[74] Li Y, St John MA, Zhou X, Kim Y, Sinha U, Jordan RC, et al. Salivary transcriptome diagnostics for oral cancer detection. Clinical Cancer Research. 2004;**10**(24):8442-8450

[75] Streckfus C, Bigler L, Dellinger T, Dai X, Kingman A, Thigpen JT. The presence of soluble c-erbB-2 in saliva and serum among women with breast carcinoma: A preliminary study. Clinical Cancer Research. 2000;**6**(6):2363-2370

[76] Wu Y, Shu R, Luo LJ, Ge LH, Xie YF. Initial comparison of proteomic profiles of whole unstimulated saliva obtained from generalized aggressive periodontitis patients and healthy control subjects. Journal of Periodontal Research. 2009;**44**(5):636-644

[77] Belinsky SA, Klinge DM, Dekker JD, Smith MW, Bocklage TJ, Gilliland FD, et al. Gene promoter methylation in plasma and sputum increases with lung cancer risk. Clinical Cancer Research. 2005;**11**(18):6505-6511

[78] Lim Y, Sun CX, Tran P, Punyadeera C. Salivary epigenetic biomarkers in head and neck squamous cell carcinomas. Biomarkers in Medicine. 2016;**10**(3):301-313

[79] Garcia-Baquero R, Puerta P, Beltran M, Alvarez M, Sacristan R, Alvarez-Ossorio JL, et al. Methylation of a novel panel of tumor suppressor genes in urine moves forward non-invasive diagnosis and prognosis of bladder cancer: A 2-center prospective study. The Journal of Urology. 2013;**190**(2):723-730

[80] Pricola Fehnel K, Duggins-Warf M, Zurakowski D, McKee-Proctor M, Majumder R, Raber M, et al. Using urinary bFGF and TIMP3 levels to predict the presence of juvenile pilocytic astrocytoma and establish a distinct biomarker signature. Journal of Neurosurgery. Pediatrics. 2016;**18**(4):396-407

[81] Genomics PE. ENCODE project writes eulogy for junk DNA. Science. 2012;**337**(6099): 1159-1161

[82] Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Research. 2012;**22**(9):1775-1789

[83] Kozomara A, Griffiths-Jones S. miRBase: Annotating high confidence microRNAs using deep sequencing data. Nucleic Acids Research. 2014;**42**(Database issue):D68-D73

[84] Catela Ivkovic T, Voss G, Cornella H, Ceder Y. microRNAs as cancer therapeutics: A step closer to clinical application. Cancer Letters. 2017;**407**:113-122

[85] Ambros V. The functions of animal microRNAs. Nature. 2004;**431**(7006):350-355

[86] Wozniak MB, Scelo G, Muller DC, Mukeria A, Zaridze D, Brennan P. Circulating MicroRNAs as non-invasive biomarkers for early detection of non-small-cell lung cancer. PLoS One. 2015;**10**(5):e0125026

[87] Takamizawa J, Konishi H, Yanagisawa K, Tomida S, Osada H, Endoh H, et al. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. Cancer Research. 2004;**64**(11):3753-3756

[88] Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell. 2006;**9**(3):189-198

[89] Yu SL, Chen HY, Chang GC, Chen CY, Chen HW, Singh S, et al. MicroRNA signature predicts survival and relapse in lung cancer. Cancer Cell. 2008;**13**(1):48-57

[90] Garofalo M, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, et al. miR-221&222 regulate TRAIL resistance and enhance tumorigenicity through PTEN and TIMP3 downregulation. Cancer Cell. 2009;**16**(6):498-509

[91] Gasparini P, Cascione L, Landi L, Carasi S, Lovat F, Tibaldi C, et al. microRNA classifiers are powerful diagnostic/prognostic tools in ALK-, EGFR-, and KRAS-driven lung cancers. Proceedings of the National Academy of Sciences of the United States of America. 2015;**112**(48):14924-14929

[92] Singh PK, Preus L, Hu Q, Yan L, Long MD, Morrison CD, et al. Serum microRNA expression patterns that predict early treatment failure in prostate cancer patients. Oncotarget. 2014;**5**(3):824-840

[93] Srivastava A, Goldberger H, Dimtchev A, Ramalinga M, Chijioke J, Marian C, et al. MicroRNA profiling in prostate cancer—the diagnostic potential of urinary miR-205 and miR-214. PLoS One. 2013;**8**(10):e76994

[94] Zheng Q, Peskoe SB, Ribas J, Rafiqi F, Kudrolli T, Meeker AK, et al. Investigation of miR-21, miR-141, and miR-221 expression levels in prostate adenocarcinoma for associated risk of recurrence after radical prostatectomy. Prostate. 2014;**74**(16):1655-1662

[95] Yaman Agaoglu F, Kovancilar M, Dizdar Y, Darendeliler E, Holdenrieder S, Dalay N, et al. Investigation of miR-21, miR-141, and miR-221 in blood circulation of patients with prostate cancer. Tumour Biology. 2011;**32**(3):583-588

[96] Daniunaite K, Dubikaityte M, Gibas P, Bakavicius A, Rimantas Lazutka J, Ulys A, et al. Clinical significance of miRNA host gene promoter methylation in prostate cancer. Human Molecular Genetics. 2017;**26**(13):2451-2461

[97] Torres-Ferreira J, Ramalho-Carvalho J, Gomez A, Menezes FD, Freitas R, Oliveira J, et al. MiR-193b promoter methylation accurately detects prostate cancer in urine sediments and miR-34b/c or miR-129-2 promoter methylation define subsets of clinically aggressive tumors. Molecular Cancer. 2017;**16**(1):26

[98] Fredsoe J, Rasmussen AKI, Thomsen AR, Mouritzen P, Hoyer S, Borre M, et al. Diagnostic and prognostic microRNA biomarkers for prostate cancer in cell-free urine. European Urology Focus. 2017

[99] Li L, Xiao B, Tong H, Xie F, Zhang Z, Xiao GG. Regulation of breast cancer tumorigenesis and metastasis by miRNAs. Expert Review of Proteomics. 2012;**9**(6):615-625

[100] Iorio MV, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Research. 2005;**65**(16):7065-7070

[101] Shin VY, Siu JM, Cheuk I, Ng EK, Kwong A. Circulating cell-free miRNAs as biomarker for triple-negative breast cancer. British Journal of Cancer. 2015;**112**(11):1751-1759

[102] Pandey AK, Zhang Y, Zhang S, Li Y, Tucker-Kellogg G, Yang H, et al. TIP60-miR-22 axis as a prognostic marker of breast cancer progression. Oncotarget. 2015;**6**(38):41290-41306

[103] Lee CH, Subramanian S, Beck AH, Espinosa I, Senz J, Zhu SX, et al. MicroRNA profiling of BRCA1/2 mutation-carrying and non-mutation-carrying high-grade serous carcinomas of ovary. PLoS One. 2009;**4**(10):e7314

[104] Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, et al. MicroRNA signatures in human ovarian cancer. Cancer Research. 2007;**67**(18):8699-8707

[105] Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;**474**(7353):609-615

[106] Chun-Zhi Z, Lei H, An-Ling Z, Yan-Chao F, Xiao Y, Guang-Xiu W, et al. MicroRNA-221 and microRNA-222 regulate gastric carcinoma cell proliferation and radioresistance by targeting PTEN. BMC Cancer. 2010;**10**:367

[107] Tsujiura M, Komatsu S, Ichikawa D, Shiozaki A, Konishi H, Takeshita H, et al. Circulating miR-18a in plasma contributes to cancer detection and monitoring in patients with gastric cancer. Gastric Cancer. 2015;**18**(2):271-279

[108] Wang R, Wen H, Xu Y, Chen Q, Luo Y, Lin Y, et al. Circulating microRNAs as a novel class of diagnostic biomarkers in gastrointestinal tumors detection: A meta-analysis based on 42 articles. PLoS One. 2014;**9**(11):e113401

[109] Hernandez YG, Lucas AL. MicroRNA in pancreatic ductal adenocarcinoma and its precursor lesions. World Journal of Gastrointestinal Oncology. 2016;**8**(1):18-29

[110] Debernardi S, Massat NJ, Radon TP, Sangaralingam A, Banissi A, Ennis DP, et al. Noninvasive urinary miRNA biomarkers for early detection of pancreatic adenocarcinoma. American Journal of Cancer Research. 2015;**5**(11):3455-3466

[111] Yu J, Li A, Hong SM, Hruban RH, Goggins M. MicroRNA alterations of pancreatic intraepithelial neoplasias. Clinical Cancer Research. 2012;**18**(4):981-992

[112] Li A, Yu J, Kim H, Wolfgang CL, Canto MI, Hruban RH, et al. MicroRNA array analysis finds elevated serum miR-1290 accurately distinguishes patients with low-stage pancreatic cancer from healthy and disease controls. Clinical Cancer Research. 2013;**19**(13):3600-3610

[113] Cote GA, Gore AJ, McElyea SD, Heathers LE, Xu H, Sherman S, et al. A pilot study to develop a diagnostic test for pancreatic ductal adenocarcinoma based on differential expression of select miRNA in plasma and bile. The American Journal of Gastroenterology. 2014;**109**(12):1942-1952

[114] Liu AM, Yao TJ, Wang W, Wong KF, Lee NP, Fan ST, et al. Circulating miR-15b and miR-130b in serum as potential markers for detecting hepatocellular carcinoma: A retrospective cohort study. BMJ Open. 2012;**2**(2):e000825

[115] Kourtidis A, Ngok SP, Pulimeno P, Feathers RW, Carpio LR, Baker TR, et al. Distinct E-cadherin-based complexes regulate cell behaviour through miRNA processing or Src and p120 catenin activity. Nature Cell Biology. 2015;**17**(9):1145-1157

[116] Ji J, Yu L, Yu Z, Forgues M, Uenishi T, Kubo S, et al. Development of a miR-26 companion diagnostic test for adjuvant interferon-alpha therapy in hepatocellular carcinoma. International Journal of Biological Sciences. 2013;**9**(3):303-312

[117] Ding X, Zhu L, Ji T, Zhang X, Wang F, Gan S, et al. Long intergenic non-coding RNAs (LincRNAs) identified by RNA-seq in breast cancer. PLoS One. 2014;**9**(8):e103270

[118] Rasool M, Malik A, Zahid S, Basit Ashraf MA, Qazi MH, Asif M, et al. Non-coding RNAs in cancer diagnosis and therapy. Non-coding RNA Research. 2016;**1**(1):69-76

[119] Zhao W, Luo J, Jiao S. Comprehensive characterization of cancer subtype associated long non-coding RNAs and their clinical implications. Scientific Reports. 2014;**4**:6591

[120] Shi Y, Li J, Liu Y, Ding J, Fan Y, Tian Y, et al. The long noncoding RNA SPRY4-IT1 increases the proliferation of human breast cancer cells by upregulating ZNF703 expression. Molecular Cancer. 2015;**14**:51

[121] Milevskiy MJ, Al-Ejeh F, Saunus JM, Northwood KS, Bailey PJ, Betts JA, et al. Long-range regulators of the lncRNA HOTAIR enhance its prognostic potential in breast cancer. Human Molecular Genetics. 2016;**25**(15):3269-3283

[122] Zhang L, Song X, Wang X, Xie Y, Wang Z, Xu Y, et al. Circulating DNA of HOTAIR in serum is a novel biomarker for breast cancer. Breast Cancer Research and Treatment. 2015;**152**(1):199-208

[123] Huang NS, Chi YY, Xue JY, Liu MY, Huang S, Mo M, et al. Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) interacts with estrogen receptor and predicted poor survival in breast cancer. Oncotarget. 2016;**7**(25): 37957-37965

[124] Chi Y, Huang S, Yuan L, Liu M, Huang N, Zhou S, et al. Role of BC040587 as a predictor of poor outcome in breast cancer. Cancer Cell International. 2014;**14**(1):123

[125] Shen Y, Katsaros D, Loo LW, Hernandez BY, Chong C, Canuto EM, et al. Prognostic and predictive values of long non-coding RNA LINC00472 in breast cancer. Oncotarget. 2015;**6**(11):8579-8592

[126] Shen Y, Wang Z, Loo LW, Ni Y, Jia W, Fei P, et al. LINC00472 expression is regulated by promoter methylation and associated with disease-free survival in patients with grade 2 breast cancer. Breast Cancer Research and Treatment. 2015;**154**(3):473-482

[127] Zhong L, Lou G, Zhou X, Qin Y, Liu L, Jiang W. A six-long non-coding RNAs signature as a potential prognostic marker for survival prediction of ER-positive breast cancer patients. Oncotarget. 2017;**8**(40):67861-67870

[128] Guo L, Peng Y, Meng Y, Liu Y, Yang S, Jin H, et al. Expression profiles analysis reveals an integrated miRNA-lncRNA signature to predict survival in ovarian cancer patients with wild-type BRCA1/2. Oncotarget. 2017;**8**(40):68483-68492

[129] Wang L, Hu Y, Xiang X, Qu K, Teng Y. Identification of long non-coding RNA signature for paclitaxel-resistant patients with advanced ovarian cancer. Oncotarget. 2017;**8**(38):64191-64202

[130] Liu R, Zeng Y, Zhou CF, Wang Y, Li X, Liu ZQ, et al. Long noncoding RNA expression signature to predict platinum-based chemotherapeutic sensitivity of ovarian cancer patients. Scientific Reports. 2017;**7**(1):18

[131] Lyu Y, Lou J, Yang Y, Feng J, Hao Y, Huang S, et al. Dysfunction of the WT1-MEG3 signaling promotes AML leukemogenesis via p53-dependent and -independent pathways. Leukemia. 2017;**31**(12):2543-2551

[132] Diaz-Beya M, Brunet S, Nomdedeu J, Pratcorona M, Cordeiro A, Gallardo D, et al. The lincRNA HOTAIRM1, located in the HOXA genomic region, is expressed in acute

myeloid leukemia, impacts prognosis in patients in the intermediate-risk cytogenetic category, and is associated with a distinctive microRNA signature. Oncotarget. 2015;**6**(31):31613-31627

[133] De Clara E, Gourvest M, Ma H, Vergez F, Tosolini M, Dejean S, et al. Long non-coding RNA expression profile in cytogenetically normal acute myeloid leukemia identifies a distinct signature and a new biomarker in NPM1-mutated patients. Haematologica. 2017;**102**(10):1718-1726

[134] Iacobucci I, Sazzini M, Garagnani P, Ferrari A, Boattini A, Lonetti A, et al. A polymorphism in the chromosome 9p21 ANRIL locus is associated to Philadelphia positive acute lymphoblastic leukemia. Leukemia Research. 2011;**35**(8):1052-1059

[135] Zhang L, Xu HG, Lu C. A novel long non-coding RNA T-ALL-R-LncR1 knockdown and Par-4 cooperate to induce cellular apoptosis in T-cell acute lymphoblastic leukemia cells. Leukemia & Lymphoma. 2014;**55**(6):1373-1382

[136] Isin M, Ozgur E, Cetin G, Erten N, Aktan M, Gezer U, et al. Investigation of circulating lncRNAs in B-cell neoplasms. Clinica Chimica Acta. 2014;**431**:255-259

[137] Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, et al. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell. 2010;**142**(3):409-419

[138] Miller CR, Ruppert AS, Fobare S, Chen TL, Liu C, Lehman A, et al. The long noncoding RNA, treRNA, decreases DNA damage and is associated with poor response to chemotherapy in chronic lymphocytic leukemia. Oncotarget. 2017;**8**(16):25942-25954

[139] Schmidt LH, Spieker T, Koschmieder S, Schaffers S, Humberg J, Jungen D, et al. The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. Journal of Thoracic Oncology. 2011;**6**(12):1984-1992

[140] Chen S, Wu H, Lv N, Wang H, Wang Y, Tang Q, et al. LncRNA CCAT2 predicts poor prognosis and regulates growth and metastasis in small cell lung cancer. Biomedicine & Pharmacotherapy. 2016;**82**:583-588

[141] Qiu M, Xu Y, Yang X, Wang J, Hu J, Xu L, et al. CCAT2 is a lung adenocarcinoma-specific long non-coding RNA and promotes invasion of non-small cell lung cancer. Tumour Biology. 2014;**35**(6):5375-5380

[142] Zhang EB, Yin DD, Sun M, Kong R, Liu XH, You LH, et al. P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression. Cell Death & Disease. 2014;**5**:e1243

[143] Sun M, Liu XH, Lu KH, Nie FQ, Xia R, Kong R, et al. EZH2-mediated epigenetic suppression of long noncoding RNA SPRY4-IT1 promotes NSCLC cell proliferation and metastasis by affecting the epithelial-mesenchymal transition. Cell Death & Disease. 2014;**5**:e1298

[144] Wang T, Qu X, Jiang J, Gao P, Zhao D, Lian X, et al. Diagnostic significance of urinary long non-coding PCA3 RNA in prostate cancer. Oncotarget. 2017;**8**(35):58577-58586

[145] Prensner JR, Iyer MK, Balbin OA, Dhanasekaran SM, Cao Q, Brenner JC, et al. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. Nature Biotechnology. 2011;**29**(8):742-749

[146] Srikantan V, Zou Z, Petrovics G, Xu L, Augustus M, Davis L, et al. PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**(22):12216-12221

[147] Mehra R, Udager AM, Ahearn TU, Cao X, Feng FY, Loda M, et al. Overexpression of the long non-coding RNA SChLAP1 independently predicts lethal prostate Cancer. European Urology. 2016;**70**(4):549-552

[148] Mehra R, Shi Y, Udager AM, Prensner JR, Sahu A, Iyer MK, et al. A novel RNA in situ hybridization assay for the long noncoding RNA SChLAP1 predicts poor clinical outcome after radical prostatectomy in clinically localized prostate cancer. Neoplasia. 2014;**16**(12):1121-1127

[149] Prensner JR, Zhao S, Erho N, Schipper M, Iyer MK, Dhanasekaran SM, et al. RNA biomarkers associated with metastatic progression in prostate cancer: A multi-institutional high-throughput analysis of SChLAP1. The Lancet Oncology. 2014;**15**(13):1469-1480

[150] Crea F, Watahiki A, Quagliata L, Xue H, Pikor L, Parolia A, et al. Identification of a long non-coding RNA as a novel biomarker and potential therapeutic target for metastatic prostate cancer. Oncotarget. 2014;**5**(3):764-774

[151] Isin M, Uysaler E, Ozgur E, Koseoglu H, Sanli O, Yucel OB, et al. Exosomal lncRNA-p21 levels may help to distinguish prostate cancer from benign disease. Frontiers in Genetics. 2015;**6**:168

[152] Zhang W, Ren SC, Shi XL, Liu YW, Zhu YS, Jing TL, et al. A novel urinary long non-coding RNA transcript improves diagnostic accuracy in patients undergoing prostate biopsy. Prostate. 2015;**75**(6):653-661

[153] El-Tawdi AH, Matboli M, El-Nakeep S, Azazy AE, Abdel-Rahman O. Association of long noncoding RNA and c-JUN expression in hepatocellular carcinoma. Expert Review of Gastroenterology & Hepatology. 2016;**10**(7):869-877

[154] Liu Z, Chang Q, Yang F, Liu B, Yao HW, Bai ZG, et al. Long non-coding RNA NEAT1 overexpression is associated with unfavorable prognosis in patients with hepatocellular carcinoma after hepatectomy: A Chinese population-based study. European Journal of Surgical Oncology. 2017;**43**(9):1697-1703

[155] Wang Z, Wu Q, Feng S, Zhao Y, Tao C. Identification of four prognostic LncRNAs for survival prediction of patients with hepatocellular carcinoma. Peer Journal. 2017;**5**:e3575

[156] El-Tawdi AH, Matboli M, Shehata HH, Tash F, El-Khazragy N, Azazy Ael S, et al. Evaluation of circulatory RNA-based biomarker panel in hepatocellular carcinoma. Molecular Diagnosis & Therapy. 2016;**20**(3):265-277

[157] Li J, Wang X, Tang J, Jiang R, Zhang W, Ji J, et al. HULC and Linc00152 Act as novel biomarkers in predicting diagnosis of hepatocellular carcinoma. Cellular Physiology and Biochemistry. 2015;**37**(2):687-696

[158] Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like

structures. Proceedings of the National Academy of Sciences of the United States of America. 1976;**73**(11):3852-3856

[159] Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One. 2012;**7**(2):e30733

[160] Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;**19**(2):141-157

[161] Pamudurti NR, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, et.al. Translation of CircRNAs. Molecular Cell. 2017;**66**(1):9-21 (e7)

[162] Schneider T, Hung LH, Schreiner S, Starke S, Eckhof H, Rossbach O, et al. CircRNA-protein complexes: IMP3 protein component defines subfamily of circRNPs. Scientific Reports. 2016;**6**:31313

[163] Granados-Riveron JT, Aquino-Jarquin G. The complexity of the translation ability of circRNAs. Biochimica et Biophysica Acta. 2016;**1859**(10):1245-1251

[164] Lai ZY, Yang Y, Yan Y, Li T, Li YS, Wang Z, et al. Analysis of co-expression networks for circular RNAs and mRNAs reveals that circular RNAs hsa_circ_0047905, hsa_circ_0138960 and has-circRNA7690-15 are candidate oncogenes in gastric cancer. Cell Cycle. 2017;**16**(23):2301-2311

[165] Huang M, He YR, Liang LC, Huang Q, Zhu ZQ. Circular RNA hsa_circ_0000745 may serve as a diagnostic marker for gastric cancer. World Journal of Gastroenterology. 2017;**23**(34):6330-6338

[166] Li P, Chen S, Chen H, Mo X, Li T, Shao Y, et al. Using circular RNA as a novel type of biomarker in the screening of gastric cancer. Clinica Chimica Acta. 2015;**444**:132-136

[167] Chen J, Li Y, Zheng Q, Bao C, He J, Chen B, et al. Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer. Cancer Letters. 2017;**388**:208-219

[168] Qin M, Liu G, Huo X, Tao X, Sun X, Ge Z, et al. Hsa_circ_0001649: A circular RNA and potential novel biomarker for hepatocellular carcinoma. Cancer Biomarkers. 2016;**16**(1):161-169

[169] Fu L, Yao T, Chen Q, Mo X, Hu Y, Guo J. Screening differential circular RNA expression profiles reveals hsa_circ_0004018 is associated with hepatocellular carcinoma. Oncotarget. 2017;**8**(35):58405-58416

[170] Huang XY, Huang ZL, Xu YH, Zheng Q, Chen Z, Song W, et al. Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-100338/miR-141-3p pathway in hepatitis B-related hepatocellular carcinoma. Scientific Reports. 2017;**7**(1):5428

[171] Shang X, Li G, Liu H, Li T, Liu J, Zhao Q, et al. Comprehensive circular RNA profiling reveals that hsa_circ_0005075, a new circular RNA biomarker, is involved in *Hepatocellular crcinoma* development. Medicine (Baltimore). 2016;**95**(22):e3811

[172] Wang X, Zhang Y, Huang L, Zhang J, Pan F, Li B, et al. Decreased expression of hsa_circ_001988 in colorectal cancer and its clinical significances. International Journal of Clinical and Experimental Pathology. 2015;**8**(12):16020-16025

[173] Huang G, Zhu H, Shi Y, Wu W, Cai H, Chen X. cir-ITCH plays an inhibitory role in colorectal cancer by regulating the Wnt/beta-catenin pathway. PLoS One. 2015;**10**(6): e0131225

[174] Xuan L, Qu L, Zhou H, Wang P, Yu H, Wu T, et al. Circular RNA: A novel biomarker for progressive laryngeal cancer. American Journal of Translational Research. 2016;**8**(2):932-939

[175] Zhong Z, Lv M, Chen J. Screening differential circular RNA expression profiles reveals the regulatory role of circTCF25-miR-103a-3p/miR-107-CDK6 pathway in bladder carcinoma. Scientific Reports. 2016;**6**:30919

[176] Zhong Z, Huang M, Lv M, He Y, Duan C, Zhang L, et al. Circular RNA MYLK as a competing endogenous RNA promotes bladder cancer progression through modulating VEGFA/VEGFR2 signaling pathway. Cancer Letters. 2017;**403**:305-317

[177] Sand M, Bechara FG, Gambichler T, Sand D, Bromba M, Hahn SA, et al. Circular RNA expression in cutaneous squamous cell carcinoma. Journal of Dermatological Science. 2016;**83**(3):210-218

[178] Li H, Hao X, Wang H, Liu Z, He Y, Pu M, et al. Circular RNA expression profile of pancreatic ductal adenocarcinoma revealed by microarray. Cellular Physiology and Biochemistry. 2016;**40**(6):1334-1344

[179] Li F, Zhang L, Li W, Deng J, Zheng J, An M, et al. Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/beta-catenin pathway. Oncotarget. 2015;**6**(8):6001-6013

[180] Bachmayr-Heyda A, Reiner AT, Auer K, Sukhbaatar N, Aust S, Bachleitner-Hofmann T, et al. Correlation of circular RNA abundance with proliferation—exemplified with colorectal and ovarian cancer, idiopathic lung fibrosis, and normal human tissues. Scientific Reports. 2015;**5**:8057

[181] Conrad KD, Niepmann M. The role of microRNAs in hepatitis C virus RNA replication. Archives of Virology. 2014;**159**(5):849-862

[182] Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, et al. Treatment of HCV infection by targeting microRNA. The New England Journal of Medicine. 2013;**368**(18):1685-1694

[183] Sempere LF, Christensen M, Silahtaroglu A, Bak M, Heath CV, Schwartz G, et al. Altered MicroRNA expression confined to specific epithelial cell subpopulations in breast cancer. Cancer Research. 2007;**67**(24):11612-11620

[184] Camps C, Saini HK, Mole DR, Choudhry H, Reczko M, Guerra-Assuncao JA, et al. Integrated analysis of microRNA and mRNA expression and association with HIF binding reveals the complexity of microRNA expression regulation under hypoxia. Molecular Cancer. 2014;**13**:28

[185] Kovalchuk O, Filkowski J, Meservy J, Ilnytskyy Y, Tryndyak VP, Chekhun VF, et al. Involvement of microRNA-451 in resistance of the MCF-7 breast cancer cells

to chemotherapeutic drug doxorubicin. Molecular Cancer Therapeutics. 2008;**7**(7): 2152-2159

[186] Sha LY, Zhang Y, Wang W, Sui X, Liu SK, Wang T, et al. MiR-18a upregulation decreases dicer expression and confers paclitaxel resistance in triple negative breast cancer. European Review for Medical and Pharmacological Sciences. 2016;**20**(11):2201-2208

[187] Luo H, Zhang H, Zhang Z, Zhang X, Ning B, Guo J, et al. Down-regulated miR-9 and miR-433 in human gastric carcinoma. Journal of Experimental & Clinical Cancer Research. 2009;**28**:82

[188] Zheng Q, Chen C, Guan H, Kang W, Yu C. Prognostic role of microRNAs in human gastrointestinal cancer: A systematic review and meta-analysis. Oncotarget. 2017;**8**(28):46611-46623

[189] Zhang Y, Guan DH, Bi RX, Xie J, Yang CH, Jiang YH. Prognostic value of microRNAs in gastric cancer: A meta-analysis. Oncotarget. 2017;**8**(33):55489-55510

[190] Brenner B, Hoshen MB, Purim O, David MB, Ashkenazi K, Marshak G, et al. MicroRNAs as a potential prognostic factor in gastric cancer. World Journal of Gastroenterology. 2011;**17**(35):3976-3985

[191] Kim CH, Kim HK, Rettig RL, Kim J, Lee ET, Aprelikova O, et al. miRNA signature associated with outcome of gastric cancer patients following chemotherapy. BMC Medical Genomics. 2011;**4**:79

[192] Lin XJ, Chong Y, Guo ZW, Xie C, Yang XJ, Zhang Q, et al. A serum microRNA classifier for early detection of hepatocellular carcinoma: A multicentre, retrospective, longitudinal biomarker identification study with a nested case-control study. The Lancet Oncology. 2015;**16**(7):804-815

[193] Li LM, Hu ZB, Zhou ZX, Chen X, Liu FY, Zhang JF, et al. Serum microRNA profiles serve as novel biomarkers for HBV infection and diagnosis of HBV-positive hepatocarcinoma. Cancer Research. 2010;**70**(23):9798-9807

[194] Ladeiro Y, Couchy G, Balabaud C, Bioulac-Sage P, Pelletier L, Rebouissou S, et al. MicroRNA profiling in hepatocellular tumors is associated with clinical features and oncogene/tumor suppressor gene mutations. Hepatology. 2008;**47**(6):1955-1963

[195] Toffanin S, Hoshida Y, Lachenmayer A, Villanueva A, Cabellos L, Minguez B, et.al. MicroRNA-based classification of hepatocellular carcinoma and oncogenic role of miR-517a. Gastroenterology 2011;**140**(5):1618-1628 (e16)

[196] Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T, et al. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and nontumoroustissues. Oncogene. 2006;**25**(17):2537-2545

[197] Kim TH, Kim YK, Kwon Y, Heo JH, Kang H, Kim G, et al. Deregulation of miR-519a, 153, and 485-5p and its clinicopathological relevance in ovarian epithelial tumours. Histopathology. 2010;**57**(5):734-743

[198] Sorrentino A, Liu CG, Addario A, Peschle C, Scambia G, Ferlini C. Role of microRNAs in drug-resistant ovarian cancer cells. Gynecologic Oncology. 2008;**111**(3):478-486

[199] Yang H, Kong W, He L, Zhao JJ, O'Donnell JD, Wang J, et al. MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. Cancer Research. 2008;**68**(2):425-433

[200] Devor EJ, Hovey AM, Goodheart MJ, Ramachandran S, Leslie KK. microRNA expression profiling of endometrial endometrioid adenocarcinomas and serous adenocarcinomas reveals profiles containing shared, unique and differentiating groups of microRNAs. Oncology Reports. 2011;**26**(4):995-1002

[201] Wu W, Lin Z, Zhuang Z, Liang X. Expression profile of mammalian microRNAs in endometrioid adenocarcinoma. European Journal of Cancer Prevention. 2009;**18**(1):50-55

[202] Kim H, Yang JM, Jin Y, Jheon S, Kim K, Lee CT, et al. MicroRNA expression profiles and clinicopathological implications in lung adenocarcinoma according to EGFR, KRAS, and ALK status. Oncotarget. 2017;**8**(5):8484-8498

[203] Tan X, Qin W, Zhang L, Hang J, Li B, Zhang C, et al. A 5-microRNA signature for lung squamous cell carcinoma diagnosis and hsa-miR-31 for prognosis. Clinical Cancer Research. 2011;**17**(21):6802-6811

[204] Landi MT, Zhao Y, Rotunno M, Koshiol J, Liu H, Bergen AW, et al. MicroRNA expression differentiates histology and predicts survival of lung cancer. Clinical Cancer Research. 2010;**16**(2):430-441

[205] Xie Y, Todd NW, Liu Z, Zhan M, Fang H, Peng H, et al. Altered miRNA expression in sputum for diagnosis of non-small cell lung cancer. Lung Cancer. 2010;**67**(2):170-176

[206] Liu R, Chen X, Du Y, Yao W, Shen L, Wang C, et al. Serum microRNA expression profile as a biomarker in the diagnosis and prognosis of pancreatic cancer. Clinical Chemistry. 2012;**58**(3):610-618

[207] Huang X, Yuan T, Liang M, Du M, Xia S, Dittmar R, et al. Exosomal miR-1290 and miR-375 as prognostic markers in castration-resistant prostate cancer. European Urology. 2015;**67**(1):33-41

[208] Brase JC, Johannes M, Schlomm T, Falth M, Haese A, Steuber T, et al. Circulating miRNAs are correlated with tumor progression in prostate cancer. International Journal of Cancer. 2011;**128**(3):608-616

[209] Lodes MJ, Caraballo M, Suciu D, Munro S, Kumar A, Anderson B. Detection of cancer with serum miRNAs on an oligonucleotide microarray. PLoS One. 2009;**4**(7):e6229

[210] Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, et al. The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. Nature Genetics. 2013;**45**(11):1392-1398