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Extracellular vesicle interactions with the external and internal exposome in mediating carcinogenesis

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ABSTRACT

The influence of environmental factors on an individual, from conception onwards, is defined as the exposome. It can be categorized into the external exposome, which includes external factors such as air pollution, chemical contaminants, and diet, and the internal exposome, which is unique to an individual, and involves age, physiology, and their genetic profile. The effect of external exposures on the internal exposome, or genetic profile, can be determined through omics analyses. However, this is often compromised due to low sample quantity and cost. Therefore, identification of other factors that can provide an insight into the cellular profile of an individual, provides an exciting avenue, and an emerging field is that of extracellular vesicles (EVs). Recently, our understanding of how cells can communicate with each other has shifted to recognise the role of EVs. EVs are secreted by all living cells, and have been identified in all biological fluids studied so far. They transport bioactive molecules (e.g., proteins, miRNAs, and DNA), and their release can be regulated by the cellular microenvironment. Analysis of EVs in respond to environmental factors might provide novel insights into the role of tumour EVs in carcinogenesis. Not only will EVs give some insight into the tumour cells themselves but they will also provide a better understanding of how cells communicate with one another, contributing to cancer progression. Moreover, characterising the content and functions of tumour-derived EVs has the potential to overcome the current challenges to improve cancer patient outcomes. For example, the identification of EVs targets for therapeutic interventions and tumour EVs biomarkers could facilitate the development of early screening for several cancers. The aim of this review, thus, is to discuss the overall role of EVs in response to the various external and internal signals in cancer. We will specifically highlight the biogenesis, secretion, and content of EVs in response to oncogenic transformation and metabolic regulators in cancer.

1. Introduction

Measure of various exposures of toxicants throughout an individual's life and their impact on health is known as the exposome (Wild, 2005). Toxicity of a chemical is dependent on its concentration within the biological system, and this remains a basic principle when discussing the exposome (Deichmann et al., 1986). This implies that if a chemical is present at high enough levels within the human body, it will be toxic. Although that is the basic principle, the concept of health effects depending on chemical exposure, has evolved, and it is now considered

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multifactorial. Christopher Wild first proposed the concept of the exposome (Wild, 2005), where the non-genetic or environmental causes of chronic diseases and their relationship with biological responses was proposed. Furthermore, a systems approach to delineate the relationship between external and internal factors was suggested to understand the onset and progression of diseases. It was noted that these exposures to external and internal agents can leave a lasting expression in our body systems. Toxins in exogenous sources such as air, water, food, drugs, and radiation, as well as endogenous processes such as inflammation, metabolism, and existing infections, and molecules such as selenium, vitamin D, adenosine, and low fat may add to the disease burden. An example of the contribution of exogenous and endogenous sources to disease burden is seen with cancers.

Sporadic changes, rather than genetic factors, are a major contributor to cancer risk. For instance, Lichtenstein and colleagues reported that genetic factors contribute only about 10% to cancer risks in twins (Lichtenstein et al., 2000). It is well known that repeated insult on the genome can accumulate and cause sporadic changes leading to the malignant transformation of normal cells (Hanahan and Weinberg, 2011). For example, cigarette smoking can leave a signature on the DNA by exposing the body's epithelial cells to at least 60 chemical carcinogens, resulting in potential DNA damage (Yamaguchi, 2019). Furthermore, ultraviolet light may also significantly alter the genome, leading to cytotoxic and mutagenic DNA lesions, and is widely associated with lung cancer and skin cancer respectively (Kalita-de Croft et al., 2016; Rastogi et al., 2010). Therefore, cancer is impacted by exogenous as well as endogenous factors, which play a significant role in cell growth and division, as well as regulating the trafficking of signals between cells.

Cell-to-cell communication is critical for all living organisms, and in cancer cells, it facilitates the exchange of information to regulate key biological processes associated with oncogenic transformation, including cell invasion and metastasis (Alharbi et al., 2019; Costa-Silva et al., 2015; Hoshino et al., 2015; Peinado et al., 2012). Recently, extracellular vesicles (EVs) have been proposed as key players in cell-to-cell communication, mainly due to their capacity to carry bioactive molecules, which can be transferred from one cell to another, to modify a wide range of biological processes (Malkin and Bratman, 2020). Recent reports have shown that EVs secreted by cancer cells can increase the migratory capabilities of target cells, ultimately inducing and aiding metastasis (Mo et al., 2021). In addition, reducing the release of EVs from tumour cells can reduce the formation of pre-metastatic niches, and spontaneous metastases (Bobrie et al., 2012; Peinado et al., 2012). Given the crucial role of EVs in cancer cell communication, it is not surprising that EVs help transfer stress signals and molecules between cancer cells, as well as normal cells, thus contributing to the internal exposome (Xu et al., 2015). A comprehensive and extraordinary role of EVs have been recently extensively discussed in two review articles (Weng et al., 2021; Zhou et al., 2021). This review particularly discusses the cancer exposome and provides insights into the role of EVs in mediating exposome related insults. The possibilities of using EVs as a tool to monitor the effects of the exposome during cancer development and progression will also be discussed.

2. EV biogenesis and heterogeneity

The concept that the external and the internal exposome affects could be mediated by EVs is not surprising as EVs have been highlighted as a valuable resource in recent literature, owing to their ability to encapsulate and transfer molecules such as lipids, proteins and nucleic acids (e.g., miRNAs), between cells, thus facilitating cell-cell communication in both physiological and pathological scenarios. This includes cell proliferation, survival, and migration, as well as neurodegenerative diseases, and cancer metastasis (Li et al., 2020; Yuana et al., 2013). Before the exposome and the EVs association could be discussed in detail, we need to briefly describe the biogenesis and heterogeneity of EVs, to grasp the overall multifaceted role of EVs in general. In this regard, the heterogeneity of extracellular vesicles termed EVs is perhaps just as extensive as the role that EVs within the human body. Extracellular vesicle is an umbrella term used for a broad population of vesicles, with a size range of approximately 40–1000 nm (Raposo and Stoorvogel, 2013; van Niel et al., 2018). EVs have a lipid bilayer membrane, and are secreted by multiple cell types, including both healthy and disease cells. Although the term extracellular vesicles are used to refer to a heterogenous population of these membrane enclosed vesicles, there are several vesicle subtypes. These vesicles can be categorized based on size, biogenesis process, and the expression of proteins associated with each subtype (van Niel et al., 2018) The two major subtypes include large vesicles, known as microvesicles, and smaller vesicles, known as exosomes. For the purposes of this review, we will use the term EVs to refer to these exosomes, and vesicles. Table 1 presents a general overview of the EV subtypes and their characteristics which is relevant to any EV related research discussion including cancer.

2.1. Biogenesis

Briefly, microvesicles include larger vesicles, generally greater than 200 nm, such as blebs, oncosomes, microparticles, and apoptotic bodies (Veziroglu and Mias, 2020). Microvesicle biogenesis is the result of an outward budding of the plasma membrane of the cell, forming a large vesicle, which is then released into the extracellular space (Chen et al., 2018). Contrastingly, exosomes are smaller extracellular vesicles, approximately 50–150 nm, and they are formed from an inward budding of the plasma membrane. This allows for the capture of membrane molecules, leading to the formation of an early endosome (Fig. 1) (Beit-Yannai et al., 2018; Ståhl et al., 2019) The early endosome then matures to a late endosomal stage and through inward invaginations of its membrane, there is a capture of the cytosolic molecules, and the formation of vesicles. Therefore, these intraluminal vesicles contain both membranous and cytosolic molecules, giving an insight into the cellular physiology. The late endosome is termed a multi-vesicular body, due to the presence of these intraluminal vesicles within it (Doyle and Wang, 2019). The multi-vesicular body can then either be degraded through fusion with a lysosome, or it can fuse with the plasma membrane, resulting in the secretion of these intraluminal vesicles, which once secreted into the extracellular space, i.e., exosomes (Doyle and Wang, 2019).

2.2. Exosome as a tool for transfer of information between cells

The exosome biogenesis process is what makes exosomes such a valuable tool, as it leads to the capture of both membranous and cytosolic molecules. It is through exosomes to gain an insight into the cellular environment, in a minimally invasive manner. Furthermore, interaction of exosomes with either neighbouring cells, or cells at distant target sites, results in cellular changes, including apoptosis, cell growth, proliferation, and migration. Exosomes can interact with target cells through multiple methods, including but not limited to direct membrane fusion, clathrin-coated endocytosis, and receptor-mediated endocytosis (Raposo and Stoorvogel, 2013; Zhang et al., 2019). The release of the exosomal contents, upon interaction with the target cells, can alter target cell behaviour, resulting in potential genotypic and phenotypic changes. These changes are mediated by the exosomal cargo which contains a range of bioactive molecules, such as small RNAs including miRNAs, proteins, and lipids (Zhang et al., 2019). Therefore, both microvesicles and exosomes can have a significant effect on cell-cell communication, and the modification of cellular behaviour and physiology. Extensive analysis of EVs and the EV cargo in recent literature has reported that they can have multiple applications, including biomarker discovery, improving understanding of disease progression, and their potential applications as therapeutic interventions for multiple diseases. Thus, EVs present a lucrative avenue for exploring the effects of the exposome, and are also major contributors to the endogenous exposome,

Table 1
Overview of the broad classification of EVs and their characteristics (Caruso and Poon, 2018; Colombo et al., 2014; Crescitelli et al., 2013; Johnstone et al., 1987; Poutsiaka et al., 1985; Raposo and Stoorvogel, 2013; Taylor et al., 1983; Tkach et al., 2018; Van der Pol et al., 2012). *Created with BioRender.com.*

Type of EV	sEVs like exosomes	mEVs like microvesicles	Apoptotic bodies/vesicles/ blebs
Size	<200 nm	~200-1000 nm	1-5 μm
Sedimentation density	100,000-200,000 g	10,000-20,000 g	1000-200,000 g
Biochemical composition	CD9, CD63, CD81, TSG101, Alix	Annexin A1	Annexin V
Cellular Origin	Multivesicular bodies	Plasma membrane budding	Apoptotic cells
References	[TKach 2018;Raposo 2013; Johnstone 1987; Colombo 2014]	[Colombo 2014; Van Der 2012; Taylor 1983; Poutsiaka 1985]	[Caruso 2018; Crescitelli 2013]

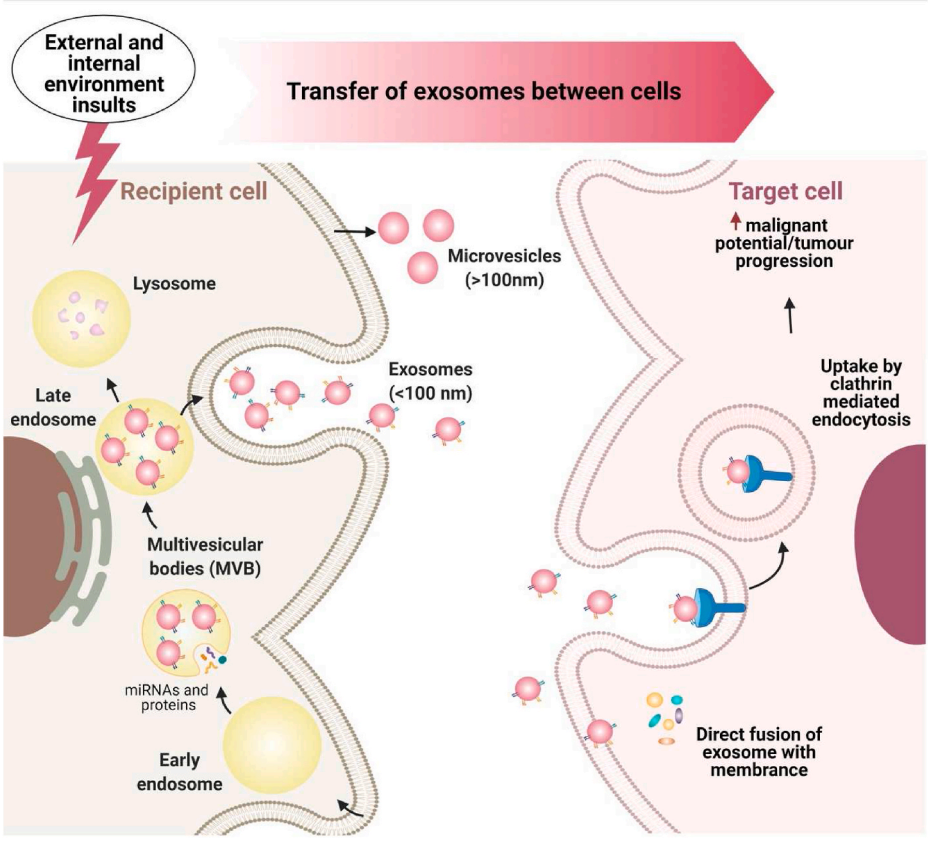

Fig. 1. Schematic representation of exposome-mediated exosomal changes and cell to cell communication. When external and internal insults occur in a particular cell (recipient cell), it triggers internal changes including exosome cargo repackaging. These exosomes may be transferred onto the target cells via direct fusion with the cell membrane or clathrin mediated endocytosis and this can lead to potential malignant transformation or cancer progression. *Created with BioRender.com.*

and their role in carcinogenesis is of significant interest.

3. Role of EVs in cancer in response to external stimuli

External stimulants such as ionizing radiation and air pollutants have been implicated in cancer progression, in addition to the genetic

mechanisms underlying cancer cell proliferation and metastasis (Perera, 1997). States and colleagues performed a connectivity study between genes involved in ovarian cancer and their interaction with a known chemical (States et al., 2014). They found some already known ovarian cancer associated carcinogens tetrachlorodibenzodioxin (Davis et al., 2000) and asbestos (Reid et al., 2011), to be associated with disease. They also found benzo [a]pyrene, co-carcinogens (tetradecanoylphorbol acetate), peroxides, heavy metals (As, Cd, Cu, Zn), epigenotoxicants (hydralizine, valproic acid), inflammation inducers (zymosan, lipopolysaccharide), steroid hormones (estradiol, progesterone, dexamethasone), dietary chemopreventives (indole-3-carbinol, curcumin) to interact with genes identified in known ovarian carcinogenesis pathways. Although the effect of carcinogens and external stimulants on disease progression is established, there are currently no methods to understand the extent to which these stimulants affect the target cells, and the pathways through which they act are not yet fully understood.

Recent studies suggest that EVs may act as a carrier of signals between stressed cells to mediate progression of the disease. Tumorigenesis may be potentiated by EVs indirectly, since exposure to carcinogens and toxins activate genotoxic effects, which results in the release of EVs carrying integrins, miRNAs, cytokines or chemokines that modulate the cellular microenvironment. For instance, when human bronchial epithelial cells (HBE) were exposed to 1.0 μM of arsenite, the major form of arsenic found in water, this triggered the release of EVs carrying miRNA-21. In addition, when normal HBE cells were exposed to these EVs, there was in increase in cell proliferation, and the expression of tensin, a target gene for miRNA-21. They confirmed the transfer of miRNA-21 by investigating the expression of PTEN, a known target gene to be repressed by miRNA-21in the treated HBE cells. The authors concluded that when miRNA-21. The authors also hypothesised that extracellular miRNA-21 transfer leads to upregulation of intracellular miRNA-21. This suggests that exogenous EVs can transfer molecules to naïve cells thus causing endogenous effects, when exposed to toxins (Xu et al., 2015).

In addition to high amounts of toxins such as arsenic, there are factors such as tobacco smoke, which is known to contain toxins. Tobacco smoke contains various toxins, one of those being NNK, or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. When male rats were exposed to NNK, there was an upregulation of miR-206 in the early stages of lung carcinogenesis. Wu et al. speculated in their study that EVs released from NNK exposed lung cells released these EVs to mediate carcinogenesis (Wu et al., 2013). Furthermore, in lung cancer, serum obtained from patients with highly metastatic cancers were shown to contain EVs that induced the epithelial to mesenchymal transition (EMT) in Human Bronchial Epithelial Cells (HBECs), evident through vimentin expression. Within the same study, migration, invasion, and proliferation was also induced in non-cancerous cells that were treated with these EVs (Rahman et al., 2016). Air pollutants such as fine particulate matter (PM2.5) imposes a threat on public health (Zanobetti and Schwartz, 2009), and its involvement in lung cancer burden has also been shown (Liao et al., 2017). When Xu et al. treated A459 cells, a lung cancer cell line, with PM2.5 and extracted exosomes secreted from these cells, they found Wnt3a to be highly abundant, indicating involvement of pro-tumorigenic Wnt-signalling pathway. Furthermore, these exosomes promoted proliferation of A549 through activation of Wnt/β-catenin signalling. Furthermore, transient knockdown of wnt3a in the cells led to reduction in the proliferation rate of the exosome treated cells (Xu et al., 2019). In melanoma, exosomes derived from aggressive tumour cells induced metastasis through the MET receptor in the bone-marrow progenitor cells, and inhibition of the MET receptor in the EVs reduced this metastatic behaviour. Briefly, tumour-derived exosomes educate the bone-marrow progenitors towards an enhanced vasculogenesis phenotype by upregulating the MET oncoprotein. Furthermore, the exosomal protein signature predicted disease progression in patients with stage 3 melanoma. They also showed the transfer of MET oncoprotein from exosomes to bone-marrow progenitor cells in-vivo. Thus, highlighting a new mechanism of metastatic progression and crosstalk (Peinado et al., 2012). UV exposed head and neck cancer cell line derived EVs conferred increased proliferation in non-irradiated cells, as well as promoted survival of recipient irradiated cells (Mutschelknaus et al., 2016). In liver cancer, cell lines exposed to arsenite released EVs which caused inflammation and the release of pro-inflammatory cytokines. Specifically, these EVs were shown to express miRNA-155, which was transferred to normal liver cells, thus promoting tumorigenesis by downregulating QKI tumour suppressing gene and releasing IL-6 and IL-8 (Chen et al., 2017). In addition, cells releasing EVs that carry miRNA-21 have been shown to be associated with platinum-resistance, which is a common phenomenon in ovarian cancer, and it is known that miRNA-21 is an EMT inducer (Alharbi et al., 2020; Crow et al., 2017). Furthermore, platinum resistant cells have been shown to harbour the SMAD-4 somatic mutation which is involved in intracellular communication, and EMT (Pohl et al., 2010).

Apart from toxins, endocrine disrupting chemicals found in our environment, food, and consumer products, may also pose a health threat, and influence exosome release, and this is well-documented. Compounds such as diethylstilbestrol and genistein may cause uterine tumours in later life if individuals are exposed to these during early life reproductive tract development. This has been hypothesised to be caused by EVs released from tumour stem cells which may be carrying important effectors of the proliferation pathway, such as Wnt (Yang et al., 2016). Whilst the effect of endocrine disrupting agents is well defined, the potential threat that nanomaterials pose is unknown. There is an increasing level of nanomaterial applications, and their utilisation has become common in both health and disease products. Kim et al. show the potential environmental impact of the use of nanomaterials such as lead sulfide quantum dots, which are used in bioimaging. Exposure of Human Embryonic kidney cells to Lead sulfide resulted in an increase in the release of EVs, with cargo that contained markers of inflammation and DNA damage, such as IL-8 and CXCL5, suggestive of onset of inflammation (Kim et al., 2015).

The potential role of EVs in mediating inflammation is emerging, with EVs derived from asthma lungs shown to have a different cargo composition compared to healthy controls (Levanen et al., 2013). Interestingly, EV miRNAs from asthma prone lungs were found to regulate the production of inflammatory mediators known to cause airway obstruction, and immune cell infiltration, such as IL-10, IL-13, IL-8. Cordazzo et al. demonstrated that smoke from cigarettes induces broncho-alveolar macrophages to release EVs that cause epithelial cells to produce proinflammatory cytokines (Cordazzo et al., 2014).

Overall, these studies highlight the emerging role of EVs in inducing carcinogenic changes due to our day-to-day life exposomes. A summary of the studies on EVs and external factors associated with carcinogenesis is presented in Table 2 and a schematic of exosomal transfer under the influence of the exposome between recipient and target cells is also illustrated in Fig. 2.

4. Role of exosomes in cancer in response to internal stimuli

During the process of tumour growth and evolution, internal stimuli could be manifested at two ends of the spectrum, one being development of cancer and the other being response to therapy. As the previous section mainly covered the development of cancer, this section will discuss the effect of internal exposome in response to therapy or development of resistance, which is a major cause of cancer-related deaths worldwide. Cancer cells acquire mechanisms to cope with internal environmental stress such as hypoxia and drug treatments, Furthermore, development of resistance to anti-cancer drugs is a commonly observed phenomenon. The content and the number of EVs change in response cancer therapeutics such as chemotherapy and radiotherapy (Bandari et al., 2018; Pascucci et al., 2014). Currently, numerous studies exist that indicate EV-mediated transfer of drug resistance in cancer, a few recent ones are highlighted in Table 3 (Aung

Table 2
Summary of the type of EVs, and the association with external stimulus (exposome), and type of cancer.

Type of EV	External stimulus	Cancer/disease phenotype	Reference
sEVs	Exosomes from metastatic cancer cells	Lung Cancer	Rahman (2016)
sEVs	Exosomes from cancer cells	Melanoma	Peinado (2012)
sEVs	Ionizing radiation	Head and Neck cancer	Mutschelknaus (2016)
sEVs	Arsenite	Liver cancer	Chen (2017)
sEVs (hypothesised)	Diethylstilbestrol, genistein	Uterine Cancer	Yang (2016)
sEVs	Lead sulfide	HEK cells; DNA damage, inflammation	Kim (2015)
mEVs	Cigarette smoke	Lung epithelial cells; inflammation	Cordazzo (2014)
sEVs	PM2.5	Lung Cancer	Xu (2019)

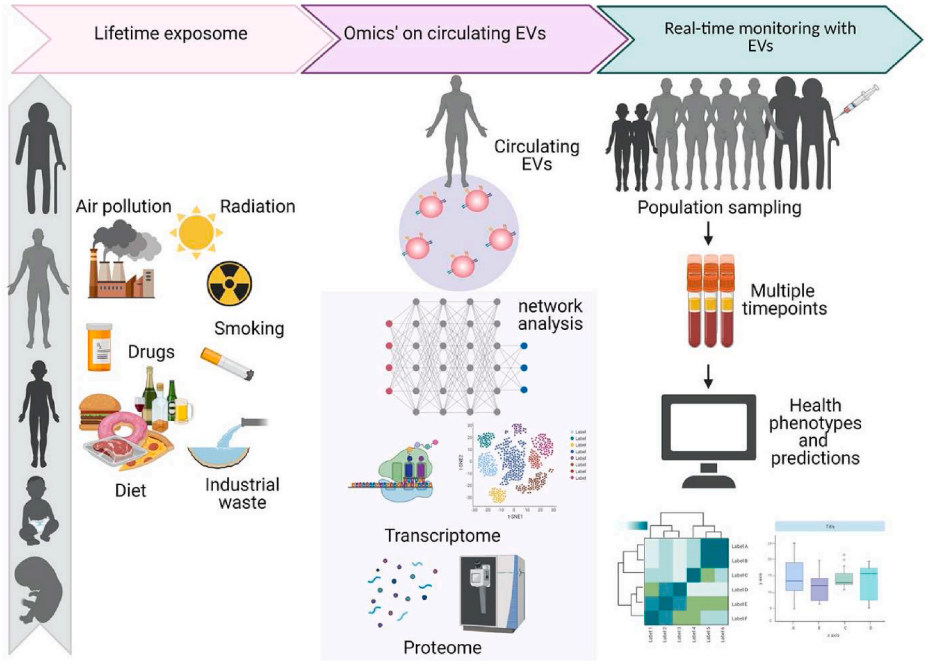

Fig. 2. Model of how EVs could be applicable in the cancer exposome field. Lifetime exposure to various insults can leave a "fingerprint" in the EVs. These circulating EVs could be subjected to a multi-omic platform for network analysis and deriving predictive signatures. Finally, a prospective population sampling study with real-time monitoring of circulating EVs, could provide data on health phenotypes, ultimately predicting outcomes. *Created with BioRender.com.*

et al., 2011; Ding et al., 2020; Liu et al., 2021; Parashar et al., 2021; Song et al., 2021; Sun et al., 2021; Wang et al., 2021; Zhang et al., 2021; Zhao et al., 2021).

Parashar and co-workers uncovered that exosomes from chemo-resistant cells carry CLPTM1L (cleft lip and palate transmembrane protein 1-like)/CRR9 (cisplatin resistance related protein 9) protein, an oncofetal protein, that confers resistance to treated ovarian and pancreatic cancer cells. They discovered that this resistance was dependent on the ectodomain shedding through EVs. Furthermore, this chemoresistance was overcome by a monoclonal antibody against CLPTM1L (Parashar et al., 2021). In solid tumours hypoxia is not rare and it is known to be involved in drug resistance and carcinogenesis (Jing et al., 2019). When Wang et al. exposed lung cancer cells to hypoxic conditions, they discovered that exosomes released from these hypoxic cells carried PKM2 and promoted glycolysis. They also demonstrated that these promoted cisplatin resistance through the expression of PKM2 in exosomes and transfer of PKM2 to tumour cells (Wang et al., 2021). Furthermore, when cancer-associated fibroblasts were co-cultured with these hypoxia-derived exosomes, they transferred PKM2 to these CAFs thus reprogramming their metabolic profile and leading to chemoresistance built up in the neighbouring cells. Abnormal metabolic activity is a salient feature of many cancers, as they require a high amount of energy and receive nutrients from the microenvironment to thrive and grow. In fact, metabolic reprogramming is a hallmark of cancer and EVs mediate a potent function within this space. The Warburg effect, named after Otto Warburg states that the rate of glycolysis in cancer cells is much higher than oxidative phosphorylation, even under sufficient oxygen condition (Warburg, 1956). Since this discovery, research has focussed on various aspects of metabolic changes, including glucose, amino acids, and lipids. There is a growing body of evidence pointing towards the facts that EVs carry different metabolites, and that these can be transferred to neighbouring cells, resulting in metabolic reprogramming and thus facilitating cancer progression (Puhka et al., 2017). Interestingly, PKM2 is a known regulator of Warburg effect and given that exosomes may play a role in this metabolic programming, it is not surprising to find hypoxia-induced exosomes expressing PKM2 which may thus lead to more glycolysis.

In gastric cancer the ribosomal protein RPS_3 was found to be highly enriched in exosomes secreted from cisplatin-resistant cells. The exosomal transfer of RPS_3 caused chemoresistance, and the RPS_3 exosomes also decreased apoptosis in sensitive cells by reducing the mitochondrial translocation of cofilin-1, this translocation is usually a necessary step for mitochondrial apoptosis (Sun et al., 2021). This study highlights the role of exosome cargo in promoting cancer cell growth under stress conditions such as chemotherapy drugs.

Interestingly, in B-cell lymphoma, when rituximab, a monoclonal antibody against B-cells was administered, lymphoma-derived exosomes were found to be enriched in CD20 which acted as a drug decoy by binding to rituximab (Aung et al., 2011). This is another facet in the role of EVs in cancer therapy induced stress which has led to overcoming the

Table 3
Summary of the EVs, and the association with internal stimulus (exposome), and type of cancer.

Type of EV	Internal stimulus	Cancer/disease phenotype	Reference
sEVs	Exosomes carry CLPTM1L/CRR9 to mediate resistance	Ovarian cancer	Parashar (2021)
sEVs	Exosomes carry miR-4443 to promote cisplatin resistance	Lung cancer	Song (2021)
sEVs	Exosomes carry circ_0000338 to promote 5-FU resistance	Colorectal cancer	Zhao (2021)
sEVs	Exosomes carry RPS3 protein to mediate cisplatin resistance	Gastric cancer	Sun (2021)
sEVs	Hypoxia-induced exosomes carry PKM2 to mediate cisplatin resistance	Lung cancer	Wang (2021)
sEVs	Exosomes carry circHIPK3 to mediate trastuzumab resistance	Breast cancer	Zhang (2021)
sEVs	Exosomes carry miR-9-5p to mediate tamoxifen resistance	Breast cancer	Liu (2021)
sEVs	Exosomes express CD20 to act as a drug decoy	B-cell Lymphoma	Aung (2011)
sEVs	Exosomes carry CircNFIX to induce temozolomide resistance	Glioma	Ding (2020)
sEVS	Hypoxic-exosomes carry miRNA-301a-3p promoting metastasis	Gastric cancer	Xia (2020)
sEVs	Hypoxic-exosomes transfer circ-RNA-133 to promote metastasis	Colorectal cancer	Yang (2020)
sEVs	Hypoxia-exosomes from glioma stem cells transfer Linc01060 glioma cells promoting progression	Glioma	Li (2021)

effect of the intervention. Tamoxifen resistance is often observed for estrogen receptor positive breast cancers and recently, Liu et al. demonstrated that this resistance was imparted by exosomal transfer of miRNA-9-5p which can target genes that enhance cyto-protection of the cells. However, this data should be considered with caution as these conclusions were based on one cell line (in-vitro and in-vivo) (Liu et al., 2021). A major obstacle in treating brain tumours such as glioma is developing resistance to the chemotherapeutic drug temozolomide (TMZ). Circular RNAs are a new class of non-coding RNAs found to be associated with health and disease (Yu et al., 2019), one of those CircNFIX has been shown to increase glioma cell proliferation by sponging miRNA-34a-5p and activating notch signalling (Xu et al., 2018). The same circRNA has been recently demonstrated to be increased in the exosomal content of temozolomide resistant glioma patients. In addition, in-vitro and in-vivo studies indicated that CircNFIX is transferred through exosomes into recipient cells causing the upregulation of the multidrug resistant protein ABCG2 and reduction of apoptosis (Ding et al., 2020).

As briefly mentioned in the previous paragraph, hypoxia is a common feature of solid tumours and is a form of cellular stress, in gastric cancer hypoxic-exosomes mediate metastasis. Specifically, carrying miRNA-301a-3p these exosomes transfer this miRNA into naive cells and promote invasion, metastasis and EMT in-vitro and in-vivo. In serum derived exosomes expression of this miRNA positively associated with peritoneal metastasis (Xia et al., 2020). Recently, circRNA-133 was found to be enriched in the plasma exosomes of colorectal cancer patients and interestingly its level increased with progression of disease. Derivation of hypoxic-exosomes containing circRNA-133 and targeting normoxic cells led to increased metastasis which could be reversed in-vivo by inhibiting circRNA-133. This circ-RNA-133 was found to be targeting tight-junction protein GEF-H1/RhoA, which are involved in remodelling of the cytoskeleton and can aid in metastasis (Yang et al., 2020). Long non-coding RNAs have also been implicated in hypoxia-derived exosomal mediated progression in glioma. Glioma stem cells under hypoxia were found to release exosomes that contain Linc010160 (long non-coding RNA). This lncRNA caused the induction of MZF1/c-myc/HIF1a axis signalling which are proteins involved in tumorigenesis and metabolic reprogramming favouring tumour growth. When the lncRNA was inhibited this axis was reduced and this led to reduced tumour burden (Li et al., 2021). Thus, overall, all these studies discussed portray exosomal transfer of unconventional toxicants due to their internal exposome leading to tumour progression and development of drug resistance.

Metabolic reprogramming through hypoxia and developing anti-cancer drug resistance is a leading cause of cancer-related mortality. The subtle interplay of the internal exposome through exosomes which impacts cancer development as well as dissipation of the treatment resistance to the surrounding microenvironment is now clear. We can conclude from multiple studies that internal exposome can impart its effect through EV-mediated mechanisms leading to cancer aggravation, growth, and metastasis and treatment resistance.

5. Future directions and exosomes as a tool to study the exposome

The field of vesicle-mediated cell-to-cell communication is of considerable contemporary interest and a burgeoning field that may provide unique insights into the aetiology of disease, early detection and treatment monitoring. To explore the exposome, it makes sense to employ an approach based upon biomonitoring (e.g., blood sampling), rather than sampling the external environment, such as air or water. As evident from the previous paragraphs', EVs circulating in the bloodstream could be an excellent candidate in exploring the exposome in any disease context, and especially in carcinogenesis. As the sources and levels of exposure time changes, we could use EVs as a real time monitoring system to identify these changes. EVs may potentially carry a signature of the toxicants which could be tracked in retrospective archival blood samples as well as in prospective clinical studies. EVs could also be carrying a host of non-traditional toxicants in the form of miRNAs, proteins, and metabolites which could indicate an abnormal state and therefore, provide us with clues as to the progression of the cancer. Exposome biomonitoring using EVs as surrogates could revolutionise cancer research by providing avenues of integrating multi-step research. For example, it could aid in direct association of EV miRNA signatures with risk factors, both exogenous and endogenous. This could also facilitate discovery of key exposomes responsible for various cancers. Ultimately, by adopting exposome biomonitoring through EVs, as a routine part of cancer research, there may be potential to help in discovering, as well as mitigating the risk factors that have a direct impact on cancer development and progression.

Understanding how EVs in response to internal and external factors regulate key events during carcinogenesis (e.g. oncogenic transformation and epithelial to mesenchymal transition) will provide an opportunity to understand the mechanisms involved in the metabolic adaptations to cancer cells, and for example to identify those patients at risk to develop chemotherapy resistance and modify their clinical management.

6. Conclusions

EVs released from cancer cells can alter the phenotype of recipient cells by transferring bioactive molecules in response to the oncogenic environment associated with the severity of the disease. Therefore, we suggest that further proteomic analyses of tumour-derived EVs are necessary to identify cancer-specific markers.

In these technologically advanced times, a fast-paced work lifestyle and a sedentary personal lifestyle is becoming a reality. With the lack of exercise and life induced stress, an individual during their life cycle, is exposed to multiple external factors (Fig. 2). This exposome influences the internal physiology triggering multiple stress signals in the body. As evident previously, EVs seem to be playing a major role in communicating these stress signals. Therefore, we could utilize these circulating EVs to study their content in-depth. This could include investigating the genome, transcriptome, and the proteome, and ultimately consolidating

this into a network, forming a multi-omics signature that could predict if an individual could develop cancer. Furthermore, another application of circulating EVs could be to study the effects of various exposomes at a multi-omic level which is currently lacking. Ultimately, we propose that future prospective studies could perform population screening.

Extracellular vesicles being such a diverse tool can open numerous opportunities in the field of cancer exposome.

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