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Contents in tumor-educated platelets as the novel biosource for cancer diagnostics

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Liquid biopsy, a powerful non-invasive test, has been widely used in cancer diagnosis and treatment. Platelets, the second most abundant cells in peripheral blood, are becoming one of the richest sources of liquid biopsy with the capacity to systematically and locally respond to the presence of cancer and absorb and store circulating proteins and different types of nucleic acids, thus called "tumor-educated platelets (TEPs)". The contents of TEPs are significantly and specifically altered, empowering them with the potential as cancer biomarkers. The current review focuses on the alternation of TEP content, including coding and non-coding RNA and proteins, and their role in cancer diagnostics.

KEYWORDS

tumor-educated platelets (TEPs), cancer diagnostics, mRNA, non-coding RNA, proteome

1 Introduction

There has been remarkable progress in the field of cancer diagnostics; however, tissue biopsy remains the most important and only method of making a definitive diagnosis. Because tissue biopsy is traumatic and infeasible for serial collection, liquid biopsy has become a hot research direction with remarkable advances including non-invasive, easy-to-obtain, and real-time monitoring (1). At present, liquid biopsy mainly focuses on cell-free DNA (cfDNA) (2), circulating tumor cells (CTCs) (3), extracellular vesicles (EVs) (4), circulating tumor RNA (5), and, more recently, tumor-educated platelets (TEPs) (6, 7). All of these biological sources present are considered to be powerful reservoirs of cancer biomarkers, contributing to early diagnosis and treatment, as well as to precision cancer medicine.

Platelets, circulating fragments of anucleate cells originating from mature megakaryocytes (MKs), are the second most abundant cell type in peripheral blood with relatively short lifespans ranging from 8 to 11 days (8) and play a crucial role in hemostasis, thrombosis, and inflammatory processes (9–11). Over the past decades, multiple pieces of evidence indicate that platelets serve much more comprehensive

functions in all steps of tumorigenesis, including tumor growth, tumor cell extravasation, angiogenesis, and metastasis (12). The interaction between platelets and tumor is the prerequisite for hematogenous metastasis (Figure 1). Platelets release many anti-angiogenic or pro-angiogenic factors when activated, which display the regulatory effect on vascular remodeling and vessel integrity, thus helping tumor cells adhere to and penetrate the endothelium (13). Upon arrival in the blood, tumor cells are covered and shielded by platelets from shear forces by lodging in the vessel wall (14), and they evade NK cells attack by impeding the immunologic recognition (15–17). Subsequently, platelets along with platelet-derived particles influence circulating tumor cells, leading to the transmission of mesenchymal-like phenotype, as well as capillary endothelium, to expedite extravasation in distant organs (18–20).

From another point of view, bidirectional tumor–platelet interactions are reciprocal and complicated on those platelets that enhance malignancies while tumors educate platelets (21–23). The education of platelets by tumor cells can be achieved in direct and indirect manners. In the bloodstream, straightforward contact occurs between molecules on platelets and tumor cells, including P-selectin (24–26), integrins (27, 28), and glycoproteins (29, 30), leading to platelet activation, so-called direct manner. Moreover, tumor cells can release metabolites extracellularly, including cytokines, chemokines, and, importantly, the extracellular vesicles, all of which serve as the indirect way to educate not only circulation platelets (31, 32) but also megakaryocytes in the bone marrow to subsequently alter platelet generation (33, 34) (Figure 1). Overall, platelets systematically and locally respond to cancer, absorbing and storing circulating proteins and different types of nucleic acids from

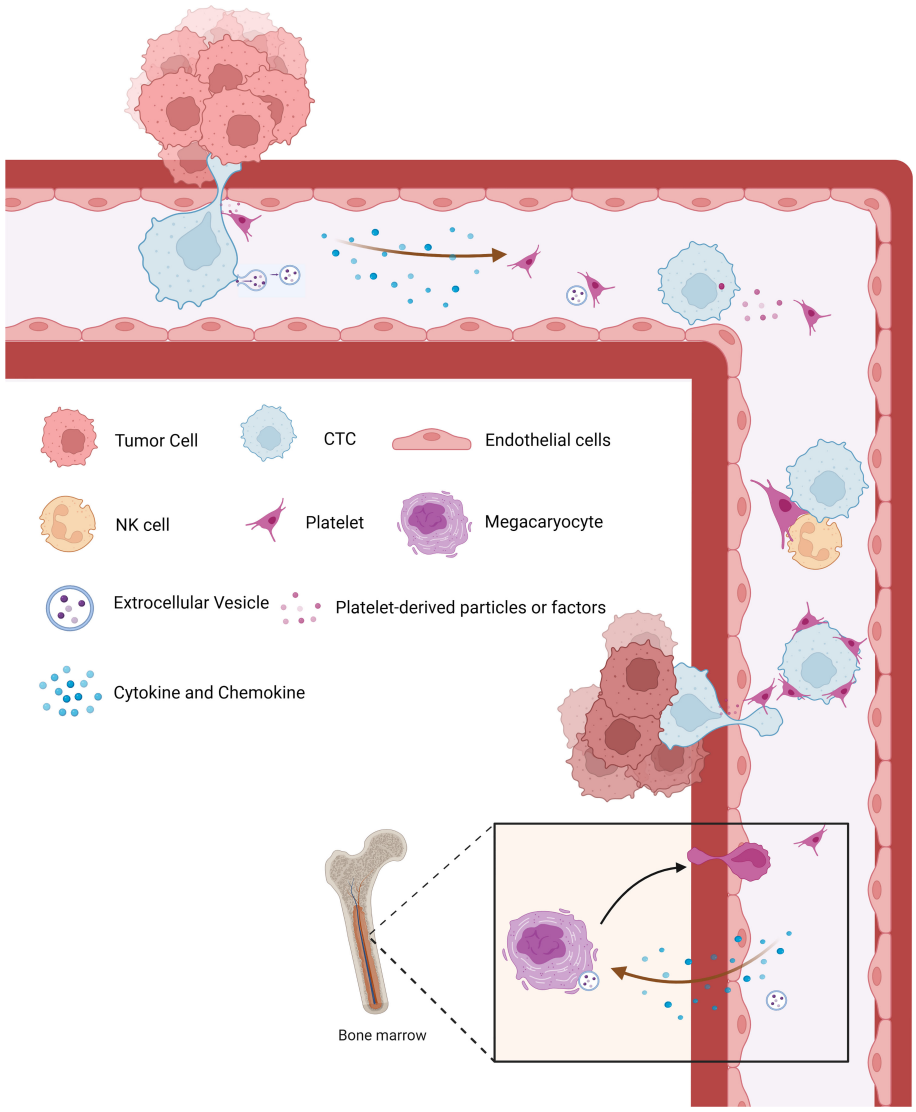

FIGURE 1
The crosstalk between cancer and platelets. Platelets are released into circulation by megakaryocytes and produce tumor-educated platelets through direct or indirect communication with tumor cells or tumor-derived biomolecules. Tumor cells can induce the activation and aggregation of platelets, which in turn secrete various factors that promote the growth and metastasis of the primary tumor. During metastasis, aggregated platelets protect CTCs from shear forces and evade immune surveillance. At the same time, platelets can recruit stromal cells to facilitate the establishment of metastatic niches and promote the metastasis of tumor cells. CTCs, circulating tumor cells.

the peripheral blood and tumor microenvironment (32), consequently sequestering tumor-specified biomolecules including RNA transcripts and proteins, which are called TEPs (7).

As high-throughput sequencing technology (35, 36) and computer identification algorithms (37, 38) have been developed in the past few years, the contents of platelets have been identified and well demonstrated. Platelets lack the nucleus and thus possess no genomic but mitochondrial DNA (39). They contain RNA molecules including coding and non-coding (40), and proteins (41), which can be not only inherited from megakaryocytes but also generated in platelets since platelets exploit functional spliceosome, ribosome, and other non-coding RNA processing mechanisms (42–44) (Figure 2). During tumor education of platelets, the contents in platelets are altered significantly and specifically in response to the presence of cancer, empowering them to serve as an important repository of potential RNA and protein biomarkers for early cancer detection (45), disease progression monitoring (7, 38), and response to treatment (46, 47).

A typical workflow for studying TEPs as biomarkers in cancer, as shown in Figure 3, consists of multiple steps. Platelet separation is the key step in the whole workflow because platelets are fragile and easily activated in the environment. Currently, the most commonly used method of platelet separation is low-speed centrifugation. Anticoagulated whole blood is centrifuged at low speed to obtain platelet-rich plasma (PRP), followed by another centrifugation to precipitate platelets at room temperature (48). D'ambrosi et al. (49) used two methods to isolate platelets, one was conventional centrifugation and the other was adding Iloprost (50 nM) to PRP, both of which obtained the lowest activation and highest purity of platelets without significant differences. The standard for high-purity platelet preparation is less than 5 nucleated cells per 10 million platelets (37) and, more importantly, to avoid platelet activation. Detection of platelet activation markers contributes significantly to the quantitative control of platelet separation. After separation, platelets are lysed for nucleic acids and protein extraction, which are then subjected to high-throughput sequencing or mass spectrometry to screen out the potential biomarkers and verified in a large-scale cohort. In the current review, attention is paid to the alternation of contents in TEPs, including coding and non-coding RNA and proteins, and their role in cancer diagnostics (Table 1).

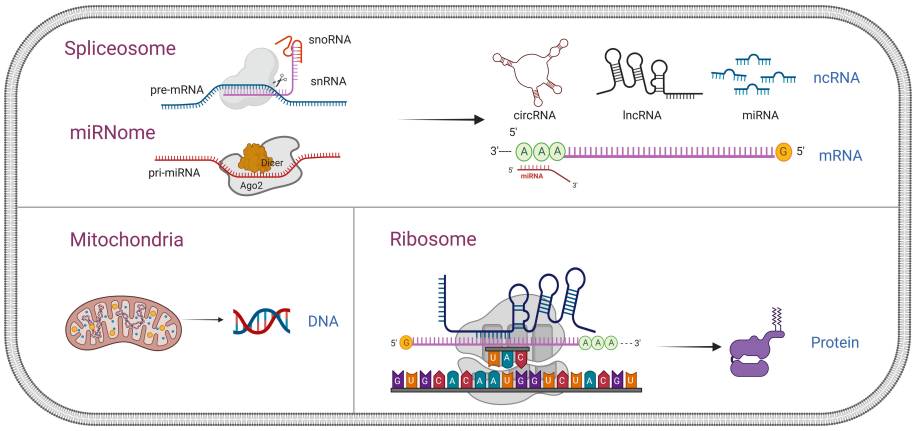

FIGURE 2
Comprehensive overview of nucleic acid and protein in platelets. Platelets lack the nucleus and thus possess no genomic but only mitochondrial DNA. They contain RNA molecules, including coding and non-coding, and proteins, which can be not only inherited from megakaryocytes but also generated in the platelets since platelets exploit functional spliceosome, ribosome, and other non-coding RNA (snRNA, snoRNA, miRNA, circRNA, and lncRNA) processing mechanisms. snRNA, small nuclear RNA; snoRNA, small nucleolar RNA; miRNA, microRNA; circRNA, circular RNA; lncRNA, non-coding RNA.

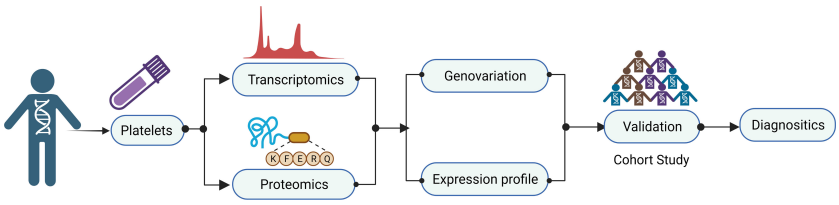

FIGURE 3
Workflow of tumor-educated platelet research for clinical applications. A typical workflow for studying TEPs as biomarkers in cancer consist of multiple steps. Platelet separation is the key step for the whole workflow because the platelets are fragile and easily activated in the environment. After separation, platelets are lysed for nucleic acids and protein extraction, which then are subjected to high-throughput sequencing or mass spectrometry to screen out the potential biomarkers and verified in a large-scale cohort. TEPs, tumor-educated platelets.

TABLE 1 Role of RNA molecules and proteins in cancer diagnosis in TEPs.

Marker type	TEP biomarkers	Tumor type	Expression	Test	Techniques	References
mRNA		Pan-cancer: NSCLC, CRC, GBM, PAAD, HBC, BRCA		Accuracy = 96%	RNA-seq, multiclass support vector machine (SVM)-based classification	(48)
	ITGA2B	NSCLC	Up	Test cohort: AUC = 0.922, validation cohort: AUC = 0.888	RNA-seq, q-PCR, ddPCR	(50)
	MAX, MTURN, HLA-B	Lung cancer	Up	AUC = 0.734, AUC = 0.787 (early lung cancer), AUC = 0.825 (MTURN mRNA as diagnostics biomarker for female lung cancer)	Microarray, q-PCR	(51)
	TIMP1	CRC	Up	AUC = 0.9583, TIPM1 mRNA carried into cancer cells by TEPs promotes cancer cell growth	RNA-seq, q-PCR	(52)
	TPM3	Breast cancer	Up	AUC = 0.9705 (diagnosis), AUC = 0.8404 (metastasis), platelet microvesicles from cancer patients promote cancer cell migration by delivering TPM3 mRNA	RNA-seq, q-PCR	(53)
	ACIN1	Lung cancer	Up	AUC = 0.608	q-PCR	(54)
MiRNA	MiR-34c-3p3p, miR-18a-5p	NPC	Up	AUC = 0.952 (miR-34c-3p3p), AUC = 0.884 (miR-18a-5p), AUC = 0.954 (combination)	q-PCR	(55)
	MiR-223	NSCLC	Up	Platelet miR-223 targeted EPB41L3 to promote A549 cell invasion		(56)
CircRNA	CircNRIP1	NSCLC	Down	p = 0.0302 (NSCLC), p = 0.0263 (late stage NSCLC), p = 0.098 (early-stage NSCLC)	RNA-seq, q-PCR	(49)
LncRNA	linc-GTF2H2-1, RP3-466P17.2, LCC-ST8SIA4-12	NSCLC		AUC = 0.781 (linc-GTF2H2-1), AUC = 0.788 (RP3-466P17.2), AUC = 0.725 (LCC-ST8SIA4-12), AUC = 0.921 (three lncRNA), early stage AUC = 0.704 (linc-GTF2H2-1), AUC = 0.771 (RP3-466P17.2), AUC = 0.768 (LCC-ST8SIA4-12), AUC = 0.895 (three lncRNA)	Microarray, q-PCR	(57)
	MAGI2-AS3, ZFAS1	NSCLC	Down	MAGI2-AS3 (AUC = 0.853, AD; AUC = 0.892, SCC); ZFAS1 (AUC = 0.780, AD; AUC = 0.744, SCC)	q-PCR	(58)
	LncRNA ROR	NPC	Down	Accuracy = 63.9%, AUC = 0.70	q-PCR	(59)
	LNCAROD, SNHG20, LINC00534, TSPOAP-AS1	CRC	Up			(60)
SnRNA	U1, U2, U5	Lung cancer	Down	AUC = 0.769 (U1), AUC = 0.840 (U2), AUC = 0.809 (U5), AUC = 0.840 (three snRNA); early stage AUC = 0.669 (U1), AUC = 0.805 (U2), AUC = 0.752 (U5), AUC = 0.826 (three snRNA)	q-PCR	(61)
SnoRNA	SNORD55	NSCLC	Down	AUC = 0.803 (NSCLC), AUC = 0.784 (early-stage NSCLC), AUC = 0.791 (LUAD), AUC = 0.759 (early-stage LUAD), AUC = 0.826 (LUSC), AUC = 0.854 (early-stage LUSC)	q-PCR	(62)
Protein	VEGF, PDGF, PF4	CRC	Up	AUC = 0.893	ELISA	(63)
	Platelet protein	OC		Late stage (III–IV): sensitivity = 96%, specificity = 88% Early stage (I–II): sensitivity = 83%, specificity = 76%, AUC = 0.831	Partial least squares discriminant analysis (PLS-DA)	(64
	Platelet count, MPV, and concentrations of VEGF, PDGF, PF4, CTAPIII, and TSP-1 in platelets and PFP	Lung cancer		AUC = 0.868	Multivariate modeling	(65)

(Continued)

TABLE 1 Continued

Marker type	TEP biomarkers	Tumor type	Expression	Test	Techniques	References
	Platelet count, MPV, and VEGF concentration in platelets	Head of pancreas cancer		AUC = 0.827	Multivariate modeling	(65)

AUC, area under the receiver operating characteristic curve; NSCLC, non-small cell lung carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; CRC, colorectal cancer; GBM, glioblastoma; PAAD, pancreatic cancer; HBC, hepatobiliary cancer; BRCA, breast cancer; ddPCR, droplet digital PCR; NPC, nasopharyngeal carcinoma; AD, adenocarcinoma; SCC, squamous cell carcinoma; OC, ovarian cancer; MPV, mean platelet volume; PFP, platelet-free plasma.

2 The coding platelet transcriptome

Platelets are anucleate and possess no available genomic DNA for the transcription of new RNA molecules but contain mitochondrial DNA with the capacity for RNA transcription activity (39). Therefore, most platelet RNAs are either inherited from the transcription of nuclear DNA in the megakaryocyte or acquired by platelets while in circulation (48). Platelets have functional spliceosomes; therefore, they can splice pre-mRNAs into mature mRNA (66). For example, Lindemann et al. (67) reported that interleukin-1β (IL-1β) pre-mRNA was spliced into intronically translatable mRNA in platelets, indicating a broad post-transcriptional regulatory mechanism for platelet mRNA expression. mRNA is the most studied type of RNA in platelets. With the development of high-throughput characterization methods, about one-third of all human genes (~5,000–9,000 genes) transcripts have been identified within platelets (68, 69). Gene ontology (GO) analysis revealed that detectable mRNAs in platelets were enriched in degranulation, coagulation, cytoskeletal dynamics, receptor binding, secretion, etc., which are biological processes closely related to well-known phenotypic activities (70, 71).

Previous studies have illuminated the diagnostic value of platelet mRNA signatures. Nilsson et al. (32) demonstrated that tumor-derived mRNAs were transferred (mutant EGFRvIII) from tumor cells to circulating platelets *in vitro* and *in vivo*. Platelets isolated from glioma and prostate cancer patients contained cancer-related RNA biomarkers EGFRvIII and PCA3, respectively, paving the way for the new potential for cancer diagnostics. Xing et al. (50) described that ITGA2B levels in TEPs were significantly higher in non-small cell lung cancer (NSCLC) patients than in controls, which could be a promising marker to improve the identification of stage I NSCLC patients and distinguish the benign and malignant pulmonary nodules. Interestingly, TIMP1 mRNA was increased in colorectal cancer (CRC) platelets, could be transferred into CRC cells by platelets, and could promote tumor growth *in vivo* and *in vitro* (52). TEP TPM3 mRNA was significantly increased in breast cancer patients, with its transfer into cancer cells mediated by platelet-derived particles to promote cancer cell migration (53). Our lab had identified a higher platelet mRNA expression of apoptotic chromatin coagulation inducing factor 1 (ACIN1) in lung cancer patients than in healthy controls (54), along with a three-platelet mRNA set—MAX, MTURN, and HLA-B—which was significantly upregulated in lung cancer patients processing a dramatically high diagnostic efficiency in female patients; the area under the curve (AUC) was 0.825 (51).

High-throughput RNA sequencing technologies have been employed in platelet RNA profile characterization. For example, the diagnostic potential of TEPs was determined by mRNA sequencing, which could distinguish tumor patients from healthy individuals with 96% accuracy, correctly identified across six different tumor types with 71% accuracy, and also ascertain MET- or HER2-positive and mutant KRAS, EGFR, or PIK3CA tumors (48). Moreover, to select robust biomarker panels for disease classification, the use of "swarm intelligence" was proposed, especially particle swarm optimization (PSO)-enhanced algorithms to analyze differences in RNA splicing isoforms of platelets from patients with NSCLC and healthy volunteers, which could achieve the accurate TEP-based detection of early and advanced NSCLC (37). More recent research has highlighted the potential properties of TEP-derived RNA panels, which correctly detected the presence of cancer in two-thirds of 1,096 blood samples from stage I–IV cancer patients and one-half of 352 stage I–III tumors, with 99% specificity in asymptomatic and 78% specificity in symptomatic controls (72).

3 The non-coding platelet transcriptome

Platelets exploit functional spliceosomes, consisting of RNA-binding protein (RBP) and small nuclear RNAs (snRNAs), including U1, U2, U4, U5, and U6. SnRNAs can bind to pre-mRNA to facilitate splicing (43). Interestingly, small nucleolar RNAs (snoRNAs) have also been described as detectable in anucleate platelets (71). SnoRNAs participate in alternative splicing of pre-mRNA in platelets other than regulation of translation in nucleated cells. Some non-coding RNA generations in the platelet also depend on post-transcriptional splicing such as circular RNAs (circRNAs). CircRNAs are generated from mature mRNAs by exonic back-splicing mediated in the spliceosome (73).

Beyond splicing, non-coding RNAs are the second post-transcriptional regulatory mechanism for platelet gene expression, including microRNAs (miRNAs), circRNAs, and long non-coding RNAs (lncRNAs). They can originate from megakaryocytes and also generate in platelets like coding RNA (40). For example, the

maturation process of miRNAs in platelets is different from that in nucleated cells. In platelets, miRNA maturation begins with unspliced pre-miRNA, and platelets contain related regulatory proteins Dicer and Argonaute 2 (Ago2), which process pre-miRNA into mature miRNA (74). Non-coding RNAs function in platelets similar to those in nucleated cells; miRNAs destabilize mRNAs and repress translation by harboring 3′-UTR but are sponged by circRNAs. Owing to diverse high-throughput techniques, such as microarrays and RNA-seq, dysregulation of non-coding RNA in TEPs can be easily observed.

3.1 MicroRNAs

MiRNAs, a class of small non-coding single-stranded RNAs with approximately 22 nucleotides in length, have highly evolutionarily conserved and tissue-specific expression patterns (75). Decades of research have demonstrated that miRNAs play a crucial role in multiple processes of cancer development. In 2009, Landry et al. (74) confirmed that human platelets contain and release miRNAs, and more than 500 different miRNAs have been identified in human platelets. In addition, human platelet miRNA profiles have extremely high stability (76), which makes platelet miRNA advantageous as diagnostic markers for tumors.

Alteration of platelet miRNA in cancer patients seems to be tumor-specific (77). Wang et al. (55) demonstrated that the expression levels of TEPs miR-34c-3p and miR-18a-5p were significantly higher in patients with nasopharyngeal carcinoma (NPC) compared to healthy subjects. The AUC value of the combined diagnosis of NPC was 0.954. However, this altered expression pattern was not found in plasma miR-34c-3p and miR-18a-5p, suggesting that the aberrances of TEP miR-34c-3p and miR-18a-5p might be the result of the "education" from NPC to platelets. The differential expression of miRNAs in platelets was also observed in a small cohort between pancreatic cancer patients and healthy subjects due to horizontal miRNA transfer between tumors and platelets. Interestingly, this differential miRNA expression was also detected between the blood and pancreatic juice-derived platelets (78). In addition, Diehl et al. (79) reported that miRNAs, including miR-19, miR-21, miR-126, miR-133, miR-146, and miR-223, could be detected in platelet-derived particles, suggesting that platelets could secrete their miRNAs through particles with potential cancer biomarkers. Similarly, the level of miR-223 in platelets of NSCLC patients was higher than in healthy subjects, and platelet-derived particles could effectively deliver miR-223 into human lung cancer cells A549, in which platelet miR-223 targeted EPB41L3 and thus promoted A549 invasion (56).

3.2 Circular RNAs

CircRNAs, the class of non-coding RNAs with a structure featuring covalently linked 3′ to 5′ ends, are highly abundant in the human genome (80). Recent studies have shown that circRNAs are differentially expressed in different types of cancer and play a crucial role in several steps of cancer initiation, tumor progression, and drug resistance (81–84). CircRNAs are significantly enriched in platelets 17- to 188-fold relative to nucleated tissues (73, 85), serving as a surrogate marker for mRNA stability in the absence of transcription relative to linear RNAs. Alhasan et al. (73) explained this phenomenon through the degradation/decay of cellular platelet RNA. CircRNAs would be more resistant to degradation by exonucleases. The abundance of circRNAs in platelets relative to megakaryocytes might attribute to circRNA generation in platelets rather than inherit from megakaryocytes (40). Thus, platelet-derived circRNAs may serve as potential novel and promising biomarkers for cancer diagnosis, treatment, and prognosis.

Ambrosi and his colleagues examined the differential circRNA profiles in platelets between NSCLC patients and asymptomatic individuals using high-throughput RNA-seq (49). A total of 4,732 circRNAs were identified, 84 of which were significantly upregulated and 327 were significantly downregulated, suggesting that the platelet circular RNA transcriptome was altered in the presence of cancer. RT-qPCR experiments confirmed that circNRIP1 was downregulated in platelet samples from advanced NSCLC, serving as an indicator of cancer progression. Moreover, a machine learning-based model algorithm was constructed for early-stage lung cancer detection based on combinatorial analysis of blood platelet-derived circRNA and mRNA signature. Combinatorial analysis, including both types of RNAs, resulted in an eight-target signature (six mRNAs and two circRNAs), enhancing the differentiation of lung cancer from controls (AUC of 0.92) (86).

3.3 Long non-coding RNA

LncRNA refers to transcripts longer than 200 nucleotides without the protein-coding ability (87). LncRNAs can act as decoys, guides, signals, or scaffolds to combine with DNA, RNA, or proteins to exert various biological functions (40). A large number of studies have shown that abnormal expression of lncRNAs in various types of cancer is associated with cancer recurrence, metastasis, and poor prognosis (88). Sun et al. (89) performed large-scale deep sequencing of human platelets, and a large number of lncRNAs were detected; the lncRNAs in TEPs are rarely reported.

Luo et al. (58) found that the levels of MAGI2-AS3 and ZFAS1 in plasma and platelets of NSCLC patients were significantly downregulated compared to those in healthy controls. Wei et al. (59) found that the TEP lncRNA-ROR of NPC patients was significantly lower than that of healthy subjects, while there was no significant difference in plasma lncRNA-ROR. Ye et al. (60) found that four lncRNA (LNCAROD, SNHG20, LINC00534, and TSPOAP-AS1) were dysregulated in TEPs of CRC patients and

could be used as potential diagnostic and discriminative biomarkers for CRC. Our group also identified TEP linc-GTF2H2-1, RP3-466P17.2, and LCC-ST8SIA4-12 as promising biomarkers for NSCLC based on lncRNA microarray and PCR validation (57), suggesting that lncRNAs derived from TEPs can be used in the diagnosis and prediction of cancer progression.

3.4 SnRNA and snoRNA

SnRNAs in the spliceosome are not merely the basal factors, ubiquitously expressed in all cells since they are required for post-transcriptional splicing, whereas snRNA levels are extremely variable across a wide range of biological conditions (90). Our lab demonstrated that TEP U1, U2, and U5 were significantly downregulated in lung cancer, which was associated with lung cancer progression, possessing favorable diagnostic efficiencies (61).

The primary function of snoRNAs is not only to guide the epigenetic modification of ribosomal RNAs (rRNAs) (91) but also to mediate pre-mRNA alternative splicing (92). For example, SNORD115 (M/HBII-52) regulated the post-transcriptional processing of serotonin 2C receptor (5-HT2CR) through alternative splicing and control of target mRNA editing (93). The presence of HTR2C pre-mRNA and splicing factors in platelets might indicate that platelet snoRNAs were involved in the mediation of alternative splicing (94). Our group reported that SNORD55 was significantly decreased in TEPs of NSCLC patients, especially of early-stage patients; it exerted a promising diagnostic value for NSCLC with an AUC of 0.803 and also improved the diagnostic accuracy of carcinoembryonic antigen (CEA) for tumor progression (62).

4 Platelet proteome

The protein content of platelets can include proteins derived from megakaryocytes, internalized from the extracellular environment, or synthesized within platelets (95). Mature and spliced RNAs can be translated into proteins in the ribosome of platelets.

Tumor cells stimulate platelet activation to release various angiogenic regulatory proteins to promote tumor angiogenesis. Peterson et al. (63) found that vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and platelet factor 4 (PF4) in platelets of 35 patients with CRC were significantly increased compared to those in 84 healthy controls. Nevertheless, this significant difference was not observed in plasma. Multivariate logistic regression analysis showed that the combined prediction of these three factors for CRC AUC was 0.893. Other studies have found elevated levels of VEGF in platelets in patients with liver cancer (96), lung cancer (97), breast cancer (98), and pancreatic cancer (65).

In recent years, advances in mass spectroscopy-based methods have greatly promoted proteomics research (41). Analysis of platelet protein expression profiles distinguished benign adnexal lesions from International Federation of Gynecology and Obstetrics (FIGO) stage III–IV ovarian cancer, and the multivariate prediction model correctly predicted seven out of eight FIGO stage I–II ovarian cancer cases (64). An analysis of proteomics in patients with early-stage lung cancer (n = 8) and pancreatic cancer (n = 4) found that 85 proteins were significantly altered in platelets in patients with early-stage lung cancer and pancreatic cancer compared to gender- and age-matched controls. After tumor removal, the expression of 81 of the 85 proteins returned to normal levels (99). Multivariate modeling was also performed using six parameters (platelet count, mean platelet volume (MPV), and concentrations of VEGF, PDGF, PF4, CTAPIII, and TSP-1 in platelets and platelet-free plasma (PFP)), and AUC was 0.868 for the diagnosis of lung cancer. The discriminatory ability of the head diagnostic model of pancreatic cancer consisting of three parameters (platelet count, MPV, and VEGF concentration in platelets) to analyze the AUC was 0.827 (65). Taken together, these studies support that platelet-derived proteins can also be used as biomarkers for cancer.

5 Conclusion

Early detection of cancer can greatly reduce the probability of distant metastasis, contributing to better treatment outcomes and the quality of life for cancer patients. In recent studies, TEPs appear to be promising candidates as biomarkers for cancer based on liquid biopsies due to the alteration of their transcripts and proteins in response to external signals (100). Platelets are the second most abundant cell in circulation after red blood cells (RBCs) and are easily isolated and counted in blood tests, making them more attractive for clinical applications (8). In recent years, more sensitive new technologies have been developed, such as high-throughput sequencing and mass spectrometry, improving the accuracy and sensitivity of TEP-based liquid biopsies (50).

The unique advantages of platelet RNA and protein in early tumor detection are exciting; however, several challenges still remain to be addressed before they can be applied in clinical trials and practice. All of the studies had small sample sizes that needed to be expanded in further studies. Platelets are easily activated during sample preparation, and the establishment of standardized procedures for TEP research, including pre-analysis processing and specific analysis steps, is far from being implemented so far but is essential and imperative. Moreover, although TEPs are widely recognized as a novel biosource for cancer diagnostics, the mechanisms that tumor educates platelets still remain unclear. Such potential confounding factors should be further addressed in a prospective clinical trial and should be standardized during the blood collection process. Taken together, further characterization of standardized procedures and mechanisms will provide new insights into the diagnostic potential of TEPs and even pave the way for personalized medicine in the future.

Author contributions

XGS designed and revised the manuscript. QZ wrote the first draft. XGS and XRS reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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