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Review Article

Pathogenic and Therapeutic Interplay of Extracellular Vesicles in Cancer and Other Diseases

Hassam Gul, Kaleem Ahmed, Aleem Ahmed

Department of Biotechnology, International Islamic University, Islamabad, Pakistan

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E: hassamgel@gmail.com

ABSTRACT

Extracellular vehicles (EVs), which can be exosomes, micro-vesicles, and apoptotic bodies, are lipid bilayer membrane vesicles implicated in inter-communication and cross talk. EVs are known to efficiently cargo DNA, lipids, oncogenic proteins, non-coding RNA, etc., which are essential in intracellular signaling, leading to their role in physiological cell-to-cell communication and pathological processes. EVs' cargo influences their role in different pathological processes. EVs have a critical role in types of cancer. However, they are not limited to cancer. They are also involved in cardiac disorders, mental diseases, atherosclerosis, lesion formation, sepsis, and renal fibrosis. The role of EVs in progression, angiogenesis, invasion, and metastasis presents an opportunity to understand the development and treatment of cancer to derive good outcomes for the patient. Moreover, EVs could be a biomarker, and their utilization can improve diagnosis and therapy for cancer.

Keywords: Micro-vesicles, Exosomes; MiRNA, Cancer Metastasis, Tumor micro-environment.

Introduction

Every cell secretes vesicles, bounded by lipid, are a process maintained and passed on evolutionary lines.[1] Initially, upon their discovery, they were linked to the elimination of unwanted compounds. Recent research on this topic of great importance revealed its role in inter-communication cross talk. Throughout the article, the term 'EVs' is used for the Extracellular Vesicles, as proposed by the International Society.[2] EVs are mainly composed of tiny lipid-bound vesicles that work as intracellular communicators by transporting their cargo, including nucleic acids, proteins relating to the plasma membrane, cytosol, and those involved in lipid metabolism.[3,4] They are highly heterogeneous, divided into three major types but not limited to: exosomes, micro-vesicles, and apoptotic bodies. The composition of EVs depends on the cell's physiological state, where their cargo can mirror the origin of the cell.[3,5] However, they share the intracellular mechanisms and sorting machinery they pass to evolve as extracellular vesicles in terms of their biogenesis.[6] Exosomes are heterogeneous molecules with a size of less than 100 nm in diameter. They are the mirror of their origin cell and produced via exocytosis pathway.[7] The inward budding of endosomal membrane forms them. Exosomes contain fusion proteins, heat shock proteins, membrane transport proteins, and tetraspanins.[8] Micro-vesicles (MVs) are formed by direct outward budding. They range from 100 nm up-to 1 nm.[7] They contain plasma membrane-associated proteins (tetraspanins), integrins, heat shock proteins, cytoskeletal proteins, and proteins containing post-translational modifications.[9] Micro-vesicles are mostly released in pathological processes, and under cellular stress.[5] Oncosomes are tumor-derived micro-vesicles where they can up-to 10µm. Normally their size ranges from 50 nm to 1000 nm in diameter.[10] Oncosomes may contain unique signatures, considering their unusual size (100-400 nm).[11] Apoptotic bodies are released by dying cells. Their size ranges from 50 nm to 5000 nm in diameter.[12]

Emerging evidence suggests that extracellular vesicles have a significant role in normal physiological biological processes but also in pathological communication. These lipid bilayer mediators of cell-to-cell communication plays a key role in disease progression, including cancer, cardiac disorders, and mental diseases. Moreover, EVs are implicated in immune suppression,[13] chemo-resistance, cell signaling, and being mediators of cancer,[14] influencing the normal cell homeostatic processes. EVs promotes cancers progression by transporting oncogenes, oncopeptides, non-coding RNAs (mRNA, miRNAs, etc.) between cancer cells and other cells in tumor microenvironments. EVs have gained much focus

of current research due to their potential as diagnostic and therapeutic biomarkers for cancer and various other diseases. This review aims to summarize the potential role of extracellular vesicles in regulating cancer pathways and hallmarks, as well as various other diseases were also discussed, including cardiac disorder, mental diseases, atherosclerosis, lesion formation, sepsis, and renal fibrosis. Moreover, the utilization of EVs as diagnostic and therapeutic biomarkers also discussed here.

1. Extracellular vesicles in hallmarks of cancer

1.1. Proliferation

In exosomes from gastric cancer (GC) patients, the micro-RNA (miRNA) profile was found in abundance compared to the control group. Particularly four were highly expressed: miR-19b-3p, miR-17-5p, miR-30a-5p, and miR-106a-5p. The same study found a higher quantity of exosome-secretion from the cancer cells than the secretion of normal cell-derived exosomes. A recent study linked the following miRNAs that were abundant in gastric cancer stem cells-derived exosomes: miR-1290 and miR-1246.[15,16]

Interaction of EVs with autologous cancer cells was found within the range of 2 hours. Internalization took place within 24 hours. The enhancement of tumor growth was afterward proved in the study. In a close-spectrum analysis, MVs size increased from 10-400 nm to 10-800 nm. Over-expression of MAGE-1, HER-2/neu mRNA was found to be explicit in IV stage cancer (GC). Additionally, MVs absolute values of zeta potential also increased. Displaying EVs own analogous characteristics with the potential to be utilized.[17] Tumor cells release EVs which is believed to have an important role in intercellular communication and in facilitation of signaling to neighboring tumor cells and distant sites via blood or other fluid transportation (Figure 1).

1.2. Metastasis

In serum-exosomes from GC patients with lymph node metastasis, 423-5p was found to be exaggerated. It can enhance proliferation and metastasis by influencing SUFU.[18] Exosomal TGF-β1 from GC patients was linked to lymphatic metastasis and Treg cell levels in lymph nodes of gastric cancer patients.[19] CD97-positive exosomes from highly lymphatic metastasis cell lines were found to enhance the capacity of metastasis compared to EVs from CD97-knockdown cells. Revealing that exosomal CD97 plays a role in GC lymphatic metastasis.[20]

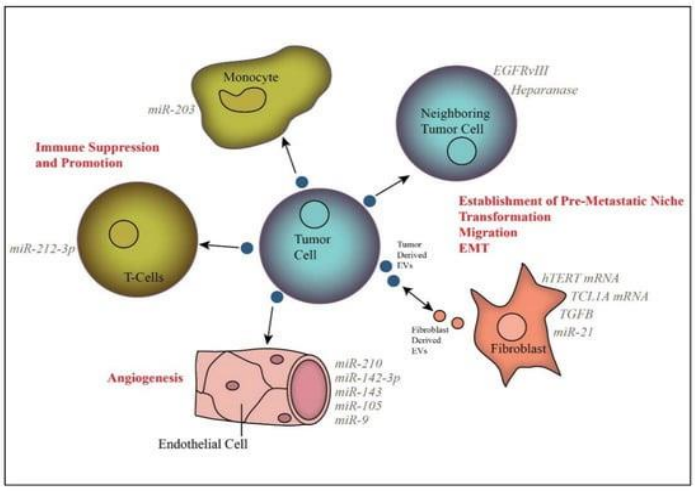

Figure 1: Extracellular vesicle-mediated transfer of specific cargo molecules alters the phenotype of recipient cells, including neighboring tumor cells, fibroblasts, endothelial cells, and immune cells.

1.3. EVs in micro-environment

CD63 has been noticed as a marker of exosomes. Its expression has been found in abundance on membranes of cancer cells and in the cytoplasm of stromal cells. A five-year survival rate was found negatively related to its expression. Forwarding the notion that CD63-positive exosomes might be facilitating the interaction between GC and stromal cells.[7,21]

1.4. EVs in Angiogenesis

MiR-130a was transferred by GC-derived exosomes into vascular cells, enhancing angiogenesis through interacting with c-MYB[22]. The range of proliferation, migration, and invasion significantly increased when GC-derived EVs were treated with human umbilical vein endothelial cells (HUVEC). [23] In another case, miR29a/c was found to mitigate VEGF expression and proliferation of vascular cells in GC, when cell-derived EVs were allowed to mediate the delivery.[24] Figure 2 explains the mechanisms

involved in the modulation of angiogenesis by endothelial EVs.

1.5. Modulating Immune

Renal cancer stem cell-derived EVs (rCSC-EVs) were noted to have an impact on dendritic cells (DC).[25] Matured DCs (differentiated with rCSC-EVs), exhibited a reduced ability to activate CD3+lymphocyte proliferation. While the release of IL-10 levels increased.[26]

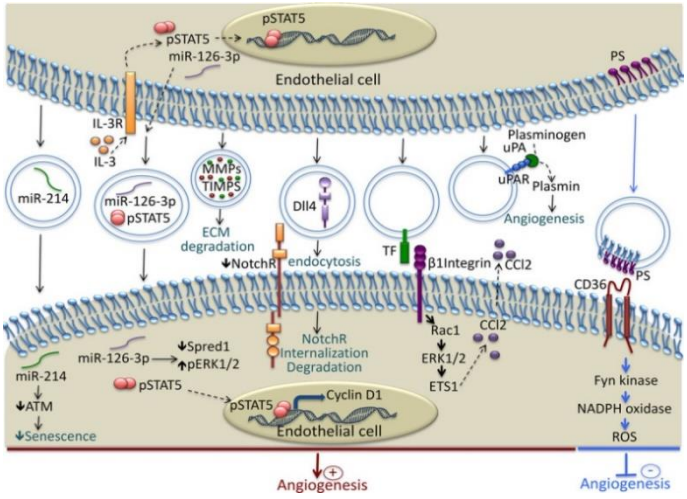

Figure 2: Main mechanisms involved in modulation of angiogenesis by endothelial EVs.

1.6. Proteomic Profiling

Proteomics studies have vesicle biogenesis and pathophysiological roles. MS-based proteomic analysis has widened the understanding of EVs protein contents. And in combination with techniques, such as chromatographic methods, their protein has been characterized.[27] A study conducted in this regard shown the changing expression of EVs under different physiological and pathological conditions. EVs transports an effector-rich proteome that had the potential to impact the functional properties of recipient cells.[28]

In one study, differentially expressed proteins (DEPS) of EVs were detected and noted to be involved in various biological processes, such as transport, migration, and cell adhesion: conveying the potential possibility of metastasis factors. DEPs from 12 different cancers, strongly overlapped, related to cancer cell proliferation and metastasis with high interaction with each other.[29]

2. EV's Cargo

2.1. EV-Associated Proteins

EVs carry different types of proteins: tetraspanins (CD63, CD9, and CD81), Rab family proteins, Tsg101, Alix, and heat shock proteins (HSP70)[30]. Proteins on their surface have been found to play a role in cancer progression. Cancer-EVs, containing programmed death-ligand (PD-L1) impede the expression of CD8 T cells in one study.[31] Tumor-derived EVs with different integrin expression patterns compared to tumor cells, guided EVs targeting point, through distinct cells and ECM molecules in specific organs.[32] Eventually showing the potential proteins that are involved in various cellular activities; such as Epithelial cell adhesion molecule (EpCAM).[33] Proteins associated with EVs can be employed in targeting specific EVs, considering their potential role, as some studies have shown. Protein caveolin-1 on EVs surface for instance was shown to reflect the degree of cancer. Caveolin-1 positive EVs increased in a mouse model compared to control mice.[34]

One study showed that CD59 and caveolin-1 co-localized with delta-catenins. They can be detected in urinary EVs of PCa patients. It is being shown that higher levels of alpha1-integrin and beta1-integrins in prostate cancer (PCa) derived EV are present compared to non-metastatic diseased patient.[35]

A newly developed ExoScreen assay exploited circulating EVs in the serum of colorectal cancer. It is based on targeting CD9, which is an EVs marker protein, doing so, validating other markers (CD63 and CD147). This technique also showed greater sensitivity compared to others, based on markers like CA19-9 and conventional ELISA.[36]

2.2. EV-Associated RNAs

Embryonic stem cells-derived EVs with mRNA were found to exhibit functions when transferred to hematopoietic progenitor cells.[37] Further studies also showed that miRNAs-positive EVs can silence genes.[38,39]

miR-181c in EVs from brain metastatic breast cancer cells was noted to lead to the destruction of the blood-brain barrier. miR-181c levels were found higher in EVs from brain metastasis patients compared to non-brain metastasis patients. Furthermore, miR-181c was found to be related to the brain metastasis of breast cancer patients.[40]

miR-21 levels were found higher in EVs from esophageal squamous cell cancer (ESCC) patients compared to patients with benign tumors.[41] While another study has shown that miR-1246 can be employed in the early diagnosis of ESCCs, with a sensitivity of 71.3%.[42] In one study, EVs from a tumor-induced pro-metastatic phenotype in bone marrow progenitors, alleviating higher expression of c-Kit, Tie2, and Met.[43,44]

2.3. Cytokines & EVs

Tumor-derived sEVs, can act as signals for the inflammatory and immune cells, which can induce the secretion of cytokines in recipient cells. Various types are noted, such as TNF, TGF, IL6. Studies have shown that melanoma-derived sEVs can play a role in metastasis and angiogenesis by inducing secretion of cytokines with pro-inflammatory effects (IL -1, GM-CSF, VEGF, and FGF).[45,46] In one study, breast cancer-sEVs prompted the NF-κB initiation,

eventually resulting in the up-regulation of several pro-inflammatory cytokines (IL-6, TNF-alpha, G-CSF, and CCL2) through TLR2 in macrophages.[47]

2.4. Cancer-Associated Fibroblasts & EVs

EVs can carry microRNAs, which can cause the shifting of normal fibroblasts (NFs) to cancer-associated fibroblasts (CAF).[48] In one study, CAFs derived EVs were found to bring changes in the context of pro-metastasis, progression, and cancer growth: CAF-secreted EVs were found as the prime regulators of the Wnt-planar cell polarity pathway in breast cancer cells.[49] A similar scenario was found to be in correlation, when EVs of similar nature, proved to be a link behind the migration of oral squamous carcinoma cells in another study.[50]

CAFs have been noted to regulate metabolic programming.[51] CAF-EVs cargo was found to effectuate glycolysis in prostate cancer. One study showed that CAF-derived EVs can be absorbed in high intensity, modulating intracellular metabolism in cancer cells. A ratio near to 35% of contribution was found in the TCA cycle fluxes of EVs, in the case of the regular supply of lactate.[52]

CAF-EVs have the potential to mediate the elicitation of OXPHOS and glycolysis through its cargo and mtDNA.[53] In one study, sEVs were found to impose Warburg-like results on recipient epithelial cells. GLUT-1-EVs were found responsible for the up-regulation of glucose, whereas increased aerobic glycolysis in tumor cells was also noted.[53]

2.5. Cancer-Associated Adipocytes-EVs

Different mechanisms have been observed concerning CAA-EVs contribution to strong cancer phenotype: enzymes involved in fatty acid oxidation, extradition through EVs[54], transfer of MMP3 to cause aggressive phenotypic changes to MMP9 activity[55], the implication of Hippo signaling pathway, through its initiation[56]. EVs from hepatocellular cancer cells were found to be absorbed by adipocytes, resulting in pro-inflammatory characteristics.[57] Through the Hippo signaling pathway, mesenchymal stem cell (MSC) differentiated adipocytes derived-sEVs can cause the proliferation of breast cancer cells.[58]

3. EVs: The potential biomarkers

Crescitelli, Lässer [59] conducted a study in an attempt to establish distinguishing characterization between extracellular vesicles, to improve the understanding of tumors. The authors find that the RNA profile was noted deeply in LD EVs (116 g/cm3), compared to HD EVs (1.176 g/cm3). EVs were isolated from tumor tissue, with a mindset to maintain the purity of the tumor blueprint. In numbers, 742 proteins were differentially expressed: ADAM10 was found in higher quantity, in small EVs, while Mitofilin was found enriched in large EVs. Like-wise, Flotillin-1 was found equally enriched in large and small LD EVs. At large, proteins related to exosomes, plasma membrane, recycling endosomes, and Golgi apparatus were found in higher quantity in the case of smaller EVs. While proteins related to endoplasmic reticulum or

mitochondrion were found enriched in larger EVs.[59]

Mitochondrial membrane proteins were found in melanoma tissue-EVs, besides the active mitochondrial enzymes in comparison to non-melanoma patients. Similar was the case in breast and ovarian cancer patients. Of significance, MT—CO2 and COX6c were highly enriched. This can be utilized concerning EVs-derived biomarkers.[60]

Persist patterns of distribution across EVs can be utilized for the discoveries of new biomarkers. Yekula, Minciacchi [61] found an enriched abundance of mRNA levels in small EVs from humans expressed a mutant form of epidermal growth factor receptor (GBM EGFRvIII), compared to the control group; whereas, larger EVs were enriched in proteins, besides the abundance of HSPA5. While tetraspanins were found enriched in small EVs. GBM EGFRvIII EVs were found different in size and quantity, compared to the control group in the mentioned study.[62]

Integrin-pattern on extracellular vesicles can be implicated in the invasion and spread of cancer. sEVs from different cancer cells were found to absorbed by organ-specific sites based on the pattern of EVs integrins.[32]

Tumor-derived b1 integrins can play an important role in EVs signaling capacity. It was found to support the anchorage-independent growth of EVs, shed by prostate cancer (PrCa) cells[62]. Besides EV-mediated stimulation of anchorage-independent growth which can abet the progression of PrCA, integrins were expressed on PrCa-derived EVs.[63,64] B1 integrin can be influential in EVs formation and secretion in prostate tumor epithelium. However, its influence can be limited to signaling, and internalization. B1 integrins-positive EVs can express CD9 and C63 biomarkers. As a whole, it impacts cancer progression.

In gastric juice-derived EVs, higher levels of methylation were noted in BarH-like 2 homeobox protein (BARHL2) from GC patients. Promoting the idea of Exosomes-BARHL2 as a potential biomarker.[65]

Extracellular vesicle-encapsulated HULC can be a biomarker for pancreatic ductal adenocarcinoma (PDAC). It was found to be capable of transporting highly regulated in liver cancer (HULC) IncRNA; therefore, supporting the invasion, migration by promoting epithelial-mesenchymal transition (EMT) in PDAC. Besides it, microRNA-133b can suppress EMT by influencing HULC. In one revelation, HULC positive-EVs expression was noted in abundance compared to healthy individual.[66]

Different studies have noted higher levels of EVs from cancer cells. Probably different mechanisms are involved. Breast cancer cell-derived EVs enriched with miR-122. MiR-1227 can induce EV shedding while hampering the shedding of smaller EVs (exosomes). It was found, it did by altering the localization of LO and exosomes, enforcing poorly migratory cancer cells and cytokines expression.[67,68]

In one study, elastin degradation products (EDP) induced blebbing that prompted the shedding of EVs, containing heat shock protein 90 (Hsp90), besides expressing tumor amoeboid phenotype. Matrikines induced cancer cell blebbing and shedding and was mediated through RPSA binding, supporting differentiation, communication between cells, and cancer progression. Several studies have noted EDPs role in metastasis: upregulates MMP-2, MTI-MMP, uPA, and Hsp90 discharge from cancer cells. Additionally, a higher level of protein (3.0 µg/mL) secretion was found to be mediated through EVs when EDPs were present compared to 0.28 µg/mL secretion of protein in absence of EDPs. Some other studies have also noted the relation of Hsp90 secretion with tumor extracellular vesicles.[69] Figure 3 depicts the use of EVs as biomarkers in both pre-clinic and clinic applications.

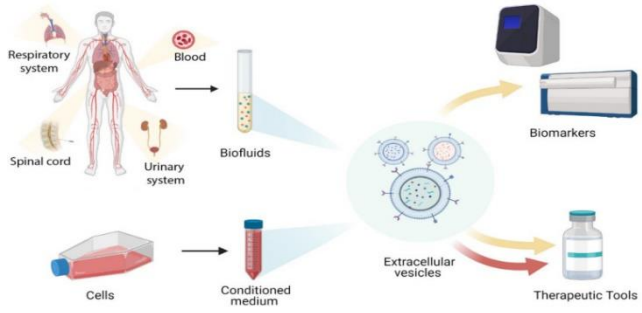

Figure 3: EVs as biomarkers or therapeutics in pre-clinic and clinic applications.

4. EV's and Cancers

4.1. Brain Tumors

The complexity of different brain tumors is attributed to intra-inter-cellular interactions concerning its microenvironment.[70] Glioblastoma does not egress central nervous system (CNS).[71] But EVs may involve, operating from non-tumor areas. EVs presence was recorded in human and murine glioma.[72] HspB5 was also identified in human cell-secreted exosomes. Further, pursue in that direction revealed that the higher release of HspB5, when treated with pro-inflammatory cytokines, displayed the possible role in tumor cell surviva.[73]

In one study, GBM-exosomes displayed high levels of reactive antibodies besides hinting at a higher production, compared to normal serum-excavated EV: supporting proliferation by inducing monocyte polarization toward M2.[74] Compared to plasma and cell lines, miRNAs were found in cerebrospinal fluid -EVs in the GBM patients: enriched with miR-21,[75]

4.2. Medulloblastoma (MB)

Exosomes from MB cells were found to contain signaling molecules (GPNMB and ERBB2), tumor transcription factor, and HNF4A. Suggesting that signaling molecules could be specific as biomarkers. Secondly, their pro-tumor progressive factors can be facilitating tumor proliferation.[76]

Proteomic studies of MB and exosomes revealed a series of proteins. But iron carrier proteins (Serotransferrin and Hemopexin) were found in the stem cells-enriched tumor population. Another study revealed that iron chelators can be used as therapeutic to cause the arrest of cells at the G1 phase in case of iron depletion.[77]

4.3. Lung cancer

MiRNAs have been found as the main components of RNA cargo of EVs, besides long-noncoding transcripts and coding transcripts.[78] Exosomes isolated from cancer patients have the potential to change target-cell transcriptome in a miRNA-mediated gene silencing (Dicer-AGO2 dependent), besides inducing oncogenic characteristics of normal epithelial cells. These cancer exosomes can also produce miRNAs within autonomy through possession of Dicer and AEO2 in their machinery.[79] EVs analysis has shed light on the heterogeneity of RNA and protein variety.[80] When seen in the reducing size, in a range of exosomes, this heterogeneity is highly reflective in the case of a complex population of miRNAs. While another finding reflected that ribonucleoprotein particles could contribute to the transport of miRNAs.[80]

EVs surface was noted to be attached by PD-L1, isolated from NSCLC patients. Expression was further found to correlate in tumor tissues.[81] mRNAs-PD-L1 can be also present. mRNAs of PD-L1 on EVs decreased in correlation with PD-L1 levels when anti-PD-1/PD-L1 therapy was applied.[82]

miRNAs transported through EVs were noted to contain the potential of anti-tumor immunity[83], besides its potential role in pro-oncogenic functions. Tumor-derived EVs, positive with miRNAs were found to allow pro-tumorigenic macrophages infiltration through induction of miRNA-103a.[84] The study revealed the significance of the blueprint of miRNAs in EVs in linkage with the prediction of response to PD-l1 therapy in NSCLC[85]. Though nucleic acids are used to express the position of NSCLC disease evolution, analyzing tumor-derived EVs, the NSCLC evolution of the disease can be further understood.

4.4. Renal Cancer

Many studies have revealed the role of renal cancer stem cell-EVs. It is found to be aiding tumor aggressiveness, angiogenesis, and immune modulation.[25] Tumor EVs can deregulate the expression of E-cadherin and β-catenin epithelial markers through disrupting adherent junction molecules[86]. Similarly, vesicular miR-23a and miR-105 can inhibit protein ZO-1 (TJP1), inevitably leading to increased vascular permeability and migration of lung cancer, metastatic breast cancers.[87] Oncogenic protein tyrosine kinase KIT-positive EVs can promote invasiveness, introducing a cancerous phenotype in progenitor smooth muscle cells.[88] One study compared normal and metastatic potential cells-EVs: finding unique protein signature and pro-

migration activity in metastatic potential cells-derived EVs.[89]

Renal cancer carcinoma (RCC) faces a poor prognosis because of high metastasis rate and resistance to chemotherapy and radiotherapy[90]. The Discovery of renal cancer stem cells has led to new possibilities in diagnosis and therapy. One study showed that rCSC-EVs contained CD105, compared to normal renal stem cells. Further analysis revealed that different sizes of RNAs were carried. Furthermore, ribosomal subunits 28 S and 18 S, usually present[91], were absent in both. miRNAs difference was also found: 24 upregulated and 33 down-regulated miRNAs were noted compared to EVs from non-stem renal cancer cells. miR-29a, miR-650, and miR-151 are also associated with metastasis[92], which were found to be dysregulated. These upregulated miRNAs were linked with metabolic processes, cell adhesion molecules, cell proliferation, and transcription.[93] This study also concluded the rCSC-EVs pro-angiogenic role. It promoted cell invasion, apoptosis resistance after doxorubicin treatment, and adhesion favorability toward renal tumor cells in endothelial cells.

MSCs are noted to be recruited in the tumor.[94] MSCs preconditioned with renal cancer stem cells (rCSC) derived-EVs displayed higher migration capacity toward the medium. Furthermore, MMP1, MMP2, MMP3, COL4A3, CXCR4, and CXCR7 were found to be upregulated. While their role is known in different spectrums of MSCs, that is to say, migration, survival, angiogenesis, tumor invasion, and immune system modulation.[95]

Enriched with azurocidin protein, EVs from renal carcinoma cells were shown to alter endothelial cell phenotype, impeding vascular morphology. Moreover, bladder cancer cells-derived EVs enriched in EDIL-3 promoted angiogenesis and migration through epidermal growth factor receptor.[96]

4.5. Over-all Survival Prediction

Circulating tumor cells in the blood are noted for their relation to overall survival (OS) prediction. Therefore, they are used as biomarkers. A study concerning circulating tumor cell-EVs found that they can be used as a predictive instrument for OS. In this study, hazard ratios (HRs) were noted to be 2.4 and 2.2 in castration-resistant prostate cancer, 2.3 and 1.9 in metastatic colorectal cancer (mCRC), 2.0 and 2.4 in non-small cell lung cancer (NSCLC). In contrast, in metastatic breast cancer (MBC), 2.7 and 2.2 were found. A higher count of CTC-EVs was aligned with exacerbating OS; furthermore, EVs were found in abundance than the CTC number. This explains the possibility of phenotypic heterogeneity.[97]

Therefore, the use of tumor-derived EVs, along with CRC, can prognostically improve diagnosis and therapy.

5. EVs & Other Diseases

5.1.1. Neurological Disorders

Through systemic injection of GAPDH siRNA-positive exosomes in mice, targeting the brain, specific gene knockdown was effectuated in the brain. Demonstrating exosome's capability to surpass blood-brain barrier.[98] A study conducted on rats showed that a fluorescently-tagged protein could be retained in EVs, in their blood, which was expressed in brain tissue.[99] In the realm of utilizing this potential, a formulation of catalase can be loaded on exosomes, acting as a drug delivery system to target neurons in Parkinson's disease.[100] However, the role of EVs in mental disorders is scant.

Exosomes can act as biomarkers of neural dysfunction, considering their ability to cross the blood-brain barrier. A study showed that exosomal miR-497 and miR-29c were upregulated in schizophrenia and bipolar patients, respectively, compared to controls[101]. The exosome's role is clarified in communication within the CNS[102]. They are implicated in neurodegenerative diseases. One study suggested that hematopoietic stem cells-derived EVs promoted hematopoietic differentiation of embryonic stem cells by re-engineering the Notch1 pathway. When EVs were treated with Suxiao Jiuxin pill (SJP), a Chinese medicine, EVs played a constructive role in the treatment of the cardiomyocytes.[103]

5.1.2. EVs in Renal Fibrosis

Its role in intracellular signaling is emphasized by the fact that EV content serves as a feedback of cells to oxidative stress, pathogens, hypoxia, and hypothermia.[104] Its content can be employed as diagnostic tools in renal fibrosis.[105,106] Blocking EVs in one finding improved the treatment of renal fibrosis (CKD).[107] The feasibility of the extraction of EVs from body fluids can be utilized as potential biomarkers in the case of renal diseases. A variety of kidney diseases is overshadowed by renal fibrosis, for example, renal parenchymal damage and non-cystic renal tissue fibrosis result from excessive accumulation of cysts, which is a characteristic of polycystic kidney disease (PKD).

Exosomes in higher quantity transported CLL2 mRNA in proteinuria renal disease to mesenchymal macrophages, resulting in the recruitment of myeloid cells and activation of mesenchymal macrophages.[108] Immunoglobulins and Platelet-derived EVs increase in SLE besides EV components, which have been found involved in glomerular deposits in LN disease patients[109]. Moreover, damaged tubular epithelial cells-derived EVs with TGF-β1 promoted adjacent fibroblasts.[110] Fibrogenic effector cells are known to play a role in the deposition of extracellular matrix.[111]

5.1.3. EVs in damage to Resident Renal Cells

EVs' role is being uncovered in implicit damage to cells, such as to mesangial and tubular epithelial cells that are an inherent characteristic of renal fibrosis development. Platelet MVs from diabetic patients induced changes that prompted the release of reactive oxygen species, prevented nitric oxide synthase and SOD activity, besides allowing higher permeability of glomerular endothelial cells. The cycle thus led to structural damage.[112]

5.1.4. EVs in Atherosclerosis

MVs are in atherosclerotic lesions from the early to the advanced stage[113]. Activation of plaque cells can prompt their shedding, considering MVs can originate from erythrocytes, leukocytes, endothelial, and smooth muscle cells.[114] Their diversified role can be in play, considering their influence on thrombosis, neoangiogenesis, endothelial homeostasis, and inflammation.

5.1.5. Exosomes in Sepsis

Sepsis is coming up as a significant cause of death in the United States. Previous studies have noted the role of miRNAs in sepsis; moreover, previous studies have also noted the results (hsa-miR-151a-3p, hsa-miR-16-5p, hsa-miR221-3p, hsa-miR-25-3p, hsa-miR-28-5p, hsa-miR-340-3p, hsa-miR-186-5p) dysregulation of miRNAs in their studies.[115,116]

miRNA-125b has been found to express higher expression beside miR-27a, which was found six times higher in expression than the previous findings.[117] MPO RNA and FOXM1 are also found dysregulated. Expressing the possibility of altered pathways related to the degradation of melanoma. Major dysregulated EVs-miRNAs can be related to inflammatory responses: the ratio in case of pathways changed during different stages of sepsis; like at enrollment, miRNAs were mostly related to redox metabolism. Explaining that EVs can be involved in inter-communication during sepsis.

Many studies reported higher production of EVs in septic patients. Some even reported lower EVs count than control groups: high platelet-derived EVs (PEV) count was noted.[118] In another study, PEV and glioma-derived EVs (GEV) count were noted higher in septic than healthy on admission. Whereas patients who died after sampling were counted with abundant PEVs on early admission[119]

Bacteria, fungi, and viruses, mainly responsible for septic shock, can also release vesicles.[120,121] *C. Albicans*-derived EVs induced synthesis of IL -10, IL -12, and nitric oxide besides increasing the expression of histocompatibility on macrophages when incubated with bone-marrow-derived macrophages.[122]

5.1.6. Exosomes in Cardiac Disease

Phospholipids and cholesterol loss from erythrocytes were documented in the 19th century. Understanding this phenomenon expanded with the identification of cellular dust and later classified as extracellular vesicles. It is potentially similar in cellular injury as a biomarker

was visibly seen, including cardiovascular diseases.[123] The study of the role of apoptotic bodies in cardiovascular disease is still rare. EVs can contribute to atherosclerosis formation and progression by taking part in lesion formation, thrombus formation, and unstable plaque progression.[124,125]

Cardiac fibroblasts can release exosomes encapsulating miRNAs that are speculated to be involved. miR-21 was identified to induce cardiomyocyte hypertrophy. It can be effectuated through silencing PDLIM5 (PDZ and LIM domain 5) protein, SORBS2 (sarcoplasmic protein sorbin and SH3 domain-containing protein 2).[126,127]

Conclusion

The extracellular vesicle role in inter-communication mechanism and cross-talk is highlighted by their ability to transfer microRNAs, resulting in a potential proliferation and forming of the metastatic niche. Their highly-heterogeneity is linked to difficulty in studying their role in disease-making and their origin. It is not clear how their cargo impacts their role in different disease-making and inter-cellular communication domains. Studies are needed to expand their role in the diagnosis and therapy of cancer and other diseases. As a transferring vehicle, their capacity can be utilized for a drug-delivery system, especially considering their ability to pass the blood-brain barrier. The shedding of EVs can be utilized as a potential biomarker explicitly linked to cancer. More studies are needed to discover potential avenues that can prompt their release. Their role in mental diseases, renal fibrosis, atherosclerosis, cardiac diseases, lesion formation, and sepsis exacerbation is coming up. More efforts are needed to find their potential aggravating role in Alzheimer's disease and Parkinson's disease progression. Their role in progression, metastasis, angiogenesis, invasion, and setting up the stage for tumor-microenvironment should be uncovered, which can be utilized in diagnosis and therapy. Extracellular vesicles have the potential to be a promising biomarker for cancer and other diseases.

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