Chapter

# Role of Exosomes in Tumor Induced Neo-Angiogenesis

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## Abstract

Exosomes are the nanovesicles, belonging to the type of extracellular vesicles (EVs), produced by normal as well as tumor cells and function as a mode in cell-to-cell communication. Tumor cells utilize various approach to communicate with neighboring cells for facilitating tumor invasion and progression, one of these approaches has been shown through the release of exosomes. Tumor-derived exosomes (TEX) have the ability to reprogram/modulate the activity of target cells due to their genetic and molecular cargo. Such exosomes target endothelial cells (among others) in the tumor microenvironment (TME) to promote angiogenesis which is an important element for solid tumor growth and metastasis. So, exosomes play a vital role in cancer invasiveness and progression by harboring various cargoes that could accelerate angiogenesis. Here first, we will present an overview of exosomes, their biology, and their role in different cancer models. Then, we will emphasis on exosomes derived from tumor cells as tumor angiogenesis mediators with a particular importance on the underlying mechanisms in various cancer origins. In the end, we will unveil the therapeutic potential of tumor derived exosomes as drug delivery vehicles against angiogenesis.

**Keywords:** extracellular vesicles, angiogenesis, exosomes, tumor, endothelial cells (ECs)

## 1. Introduction

Tumor microenvironment interacts with tumor cells, creating an environment to suppress or contribute towards tumor development and progression [1]. For the tumor development, inflammation and angiogenesis are the processes which play vital roles from initial to the advanced stages of cancer [2]. Extreme angiogenesis and neo-angiogenesis play a fundamental role in tumor progression, which is driven by various pro-and anti-angiogenic factors [3]. There are different ways for tumor cells to communicate with adjacent cells/tissues for facilitating tumor progression; one of these is through exosomes [4, 5]. Exosomes can transport various biomolecules like DNA

fragments, mRNAs, noncoding RNAs, proteins, and lipids from a source cell to target/recipient cells that can enhance angiogenesis, which play a significant role in cancer progression [6]. There are evidences that various noncoding RNAs, particularly microRNAs and long non-coding RNAs (lncRNAs) play significant role in the regulation of angiogenesis [7]. Thus, alteration of angiogenesis has become a striking approach for development of effective cancer therapy [1].

## 2. Extracellular vesicles (EVs)

Prior to the discovery of exosomes it was assumed that the transmission of information between mammalian cells occurs in an indirect manner. In 1983, two pioneer studies carried out on the differentiation of reticulocytes into mature erythrocytes, reported release of transferrin receptors into extracellular space in form of small vesicles, which were later termed as "exosomes" by R.M. Johnstone [6, 8–10]. EVs are vesicles enclosed with phospholipid bilayer secreted in the extracellular matrix. Initially, they were initially considered as "garbage dumpsters" but now they are popularly being referred as "signal boxes" [11]. The presence of extracellular vesicles in solid tissue, physiological fluid, and cell culture supernatants has been demonstrated by a number of studies [12]. EV's are broadly categorized into different subtypes like microsomes, microvesicles, retrovirus-like particles and apoptotic bodies, different from each other on the basis of size, surface markers and their mode of biogenesis [13]. Extracellular vesicle is a collective term for exosomes and microvesicles. Microvesicles originate from through outward budding and fusion of plasma membrane whereas, exosomes are released via endocytosis and fusion with plasma membrane [14]. Exosomes are the smallest (30–100 nm) subpopulation of EVs. CD9, CD63 and Alix are the specific surface markers for these exosomes [13]. Exosome serve as important cell communication regulators and have gained more attention among all the diverse types of extracellular vesicles because they represent a more homogenous set of vesicular population more closely representing the parent cell of origin [15].

### 2.1 Exosome biogenesis

Exosomes are endosome derived extracellular vesicles. Multivesicular endosomes (MVEs) or multivesicular bodies (MVBs) are secreted via intracellular secretion pathway, from the plasma membrane. Early endosomes develop into MVBs which fuse with the cell membrane and release the exosomes or else undergoes degradation in lysosomes and autophagosomes. They are cup-or disc-shaped when observed under electron microscopy having a diameter of 30–150 nm [11, 16]. Various proteins and molecules like (ALIX, VPS4, and TSG101) are some of the major proteins involved in exosome biogenesis, content assembly and their secretion via endosomal sorting complex [16]. Exosome biogenesis supposedly occurs via two major pathways: Endosomal sorting complexes required for transport (ESCRT) dependent and ESCRT independent. The ESCRT dependent process includes ESCRT complex (0, I, and II) which are involved in recognizing and sequestering the ubiquitinylated proteins on the endosomal membrane. Exosomes are formed by membrane remodeling, involving bud formation by invagination of this endosomal membrane [17]. ESCRT independent pathway involves tetraspanins such as CD63 and lipid metabolism enzymes like neutral sphingomyelinase (nSMase) and rab family protein consisting of more than 60 GTPases that regulate intracellular trafficking of exosomes [16]. Anchoring of MVBs

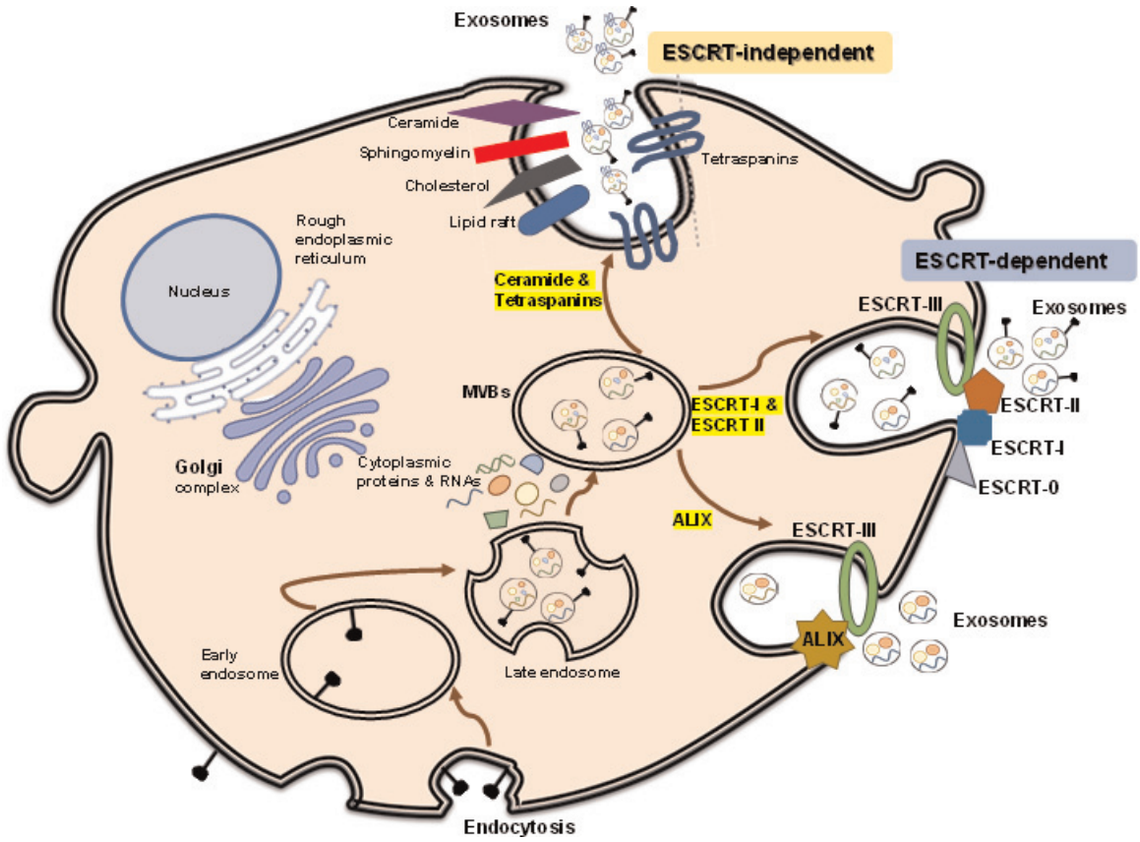


**Figure 1.**
*Schematic representation of exosome biogenesis and secretion from eukaryotic cells. Exosome's formation starts with endocytosis, which involves inward budding of plasma membrane, leading to the formation of early and late endosomes. Further, small vesicles are generated by inward budding of late endosomes and forming multivesicular bodies (MVBs). The ultimate fate of MVBs can be either fusion with lysosome for degradation or fusion with plasma membrane to release exosomes. The exosome formation from MVBs proceeds through ESCRT-dependent and ESCRT-independent pathways. ESCRT-dependent pathway involves various ESCRT proteins like (ESCRT 0, I, II, and III) and ESCRT-independent includes lipids (ceramide) and the tetraspanins.*

and transportation of different exosomes is carried out by different RAB subtypes proteins. Early endosome transportation involves RAB5 and RAB21 proteins to mediate endocytosis pathway from early to late endosome and then to lysosome for degradation involves RAB7 protein. Tumor-associated vesicle trafficking requires a vital protein that is RAB27 and it is highly expressed in several tumors. Other than this, various RAB proteins which include RAB 3,11,26,27, 35, 37 and RAB 38 are linked with the exocytic pathway of vesicle trafficking [11]. RAB27 helps in the release of exosomes from mature endosomes enriched in TSG101, ALIX and CD63 whereas RAB11 & RAB35 are associated with the release of early nuclear endosomes which are enriched with PLP, Wnt and TfR. Finally, MVBs fused with the plasma membrane and exosomes are excreted out in the extracellular environment [12]. Diagrammatic representation of exosome biogenesis and secretion has been shown in **Figure 1**.

## 2.2 Exosomal content

Exosomes are nanovesicles enriched with a repertoire of biomolecules like proteins, nucleic acids and lipids [16]. Exosomes are dynamic and heterogeneous in nature with respect to their content which majorly depends on their cellular origin, pathological and physiological state of the parent cells. Exosomes from different cell types are enriched specifically in proteins like Alix, Tsg101, integrins, Rab GTPases,

tetraspanins (CD9) and (CD63), MHC class II proteins and heat shock proteins (HSP90, HSP70), which alsoserve as exosome marker proteins [16, 18]. Besides these, exosomes are also enriched with double-stranded DNA's and RNA population of different classes such as microRNA (miRNA), long noncoding RNA (lncRNA) [19]. ExoCarta and Vesiclepedia (http://microvesicle.org/), databases have cataloged the RNA, protein and lipid content of exosomes derived from different sources.

## 3. Mechanisms involved in exosomes-induced angiogenesis

Tumor derived exosomes (TEXs) have been shown to play a significant role in tumor progression by accelerating angiogenesis [20]. New blood vessel formation occurred when angiogenic signaling pathways are activated by tumor-derived exosomes, when they are up taken by normal ECs [21]. Exosomal cargo once internalized into recipient cells present in the tumor microenvironment, can regulate their fate, function, and phenotype [22, 23]. Tumor cell derived exosomal cargo can activate/inhibit the various signaling pathway in ECs via receptor-ligand interaction [24]. There are several studies represent multiple avenues in which cancer-derived exosomes exert pro-angiogenic effects on ECs. Till date, the different signaling pathways that are involved in exosomes-induced angiogenesis are poorly known. However, the exosomal cargo which is involved in tumor progression and angiogenesis have been documented. Role of TEXs cargoes which is involved in tumor angiogenesis is showed in **Figure 2**. Also, a list of all mRNAs, proteins, and noncoding RNAs which are found in TEXs for regulating tumor angiogenesis are listed in **Table 1**.

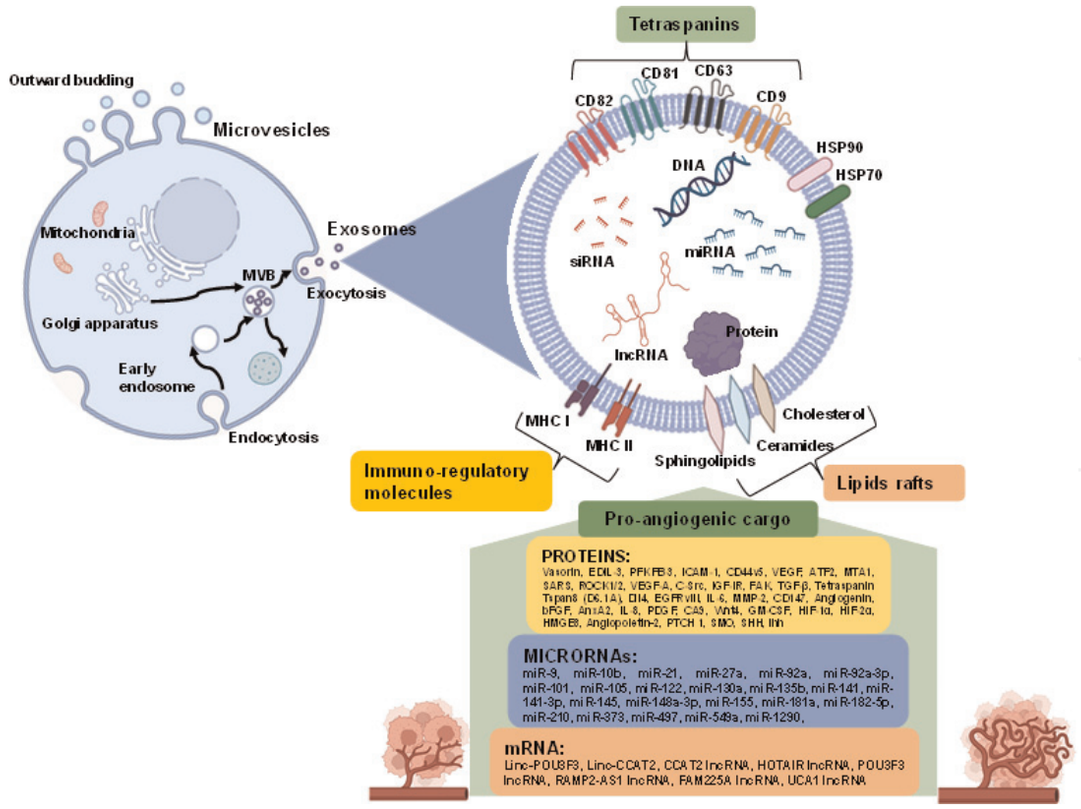


**Figure 2.**
*Tumor derived exosomes as carrier of pro-angiogenic cargo from different cancer models promote neo-angiogenesis. Tumor-derived exosomes are enriched in proangiogenic proteins, mRNAs, miRNAs, and long noncoding RNAs which are transferred to recipient endothelial cells and activate various angiogenic signaling pathways involved in different angiogenesis process via cell proliferation, migration, and invasion.*

| Exosomal cargo | Tumor type | Type of study (*in-vitro/ in-vivo*) | Cell lines | Target cell | Mechanisms | Function | References |
|---|---|---|---|---|---|---|---|
| EGFRVIII | Glioma cells | Both | U373Viii | U373 and HUVECs | Increase in the VEGF gene expression, by activating the MAPK and Akt pathways | Pro-angiogenesis | [25, 26] |
| Dll4 | Glioma cells | Both | U87MG | HUVEC | Inhibition of notch signaling | Pro-angiogenesis | [27] |
| POU3F3 lncRNA | Glioma cells | *In-vitro* | A172, U87-MG, U251 and T98G | HBMVECs | Increasing the expression of bFGF, VEGFA and bFGFR in ECs | Pro-angiogenesis | [22] |
| HOTAIR lncRNA | Glioma cells | *In-vitro* | A172 | HBMVECs | Increase in the VEGFA expression of ECs | Pro-angiogenesis | [28] |
| CCAT2 lncRNA | Glioma cells | *In-vitro* | A172, U87-MG, U251, and T98G | HUVECs | Increase in the expression of VEGFA and other angiogenic signaling molecules of ECs and decrease in the apoptosis process | Pro-angiogenesis | [29] |
| IL-8, PDGF | Glioblastoma | *In-vitro and ex-vivo* | U87MG | ECs | PI3K/AKT signaling | Pro-angiogenesis | [30] |
| VEGF-A | Glioblastoma | *In-vitro* | GSC | Brain microvascular ECs | Enhancement in angiogenic potential of brain ECs | Pro-angiogenesis | [31] |
| miR-148a-3p | Glioblastoma | *In-vitro* | U-138-MG, U251-MG, and HEK-293 T | HUVECs | Activating the EGFR/MAPK signaling pathway by inhibiting ERRFI1 | Pro-angiogenesis | [32] |
| miR-182-5p | Glioblastoma | *In-vitro* | U-251MG, H4, A-172, U-118MG, LN-18, and U-87MG | HUVECs | Targeting Kruppel-like Factor 2 and 4 | Pro-angiogenesis | [33] |
| miR-10b | Breast cancer | *In-vitro* | MCF-7 and MM-231 | HMLE | Suppression of HOXD10 and KLF4 proteins level | Promotes cell invasion | [34] |
| miR-373 | Breast cancer | *In-vitro* | MCF-7 and MM-231 | ECs | Wnt/β-catenin signaling | Pro-tumorigenesis | [35] |
| miR-122 | Breast cancer | Both | MCF-10A and MM-231 | Normal cells in pre metastasic niche | Downregulation of PKM | Promotes metastasis, before angiogenesis | [36] |
| miR-497 | Breast cancer | Both | MCF-7 | HUVECs | Decrease in the expression of VEGF and HIF-1 | Anti-angiogenesis | [37] |
| AnxA2 | Breast cancer | Both | MCF10A and MM-231 | Macrophages and ECs | Generation of plasmin | Pro-angiogenesis | [38] |
| miR-210 | Breast cancer | Both | 4 T1 | ECs | Upregulation of VEGF | Pro-angiogenesis | [39] |
| miR-145 | Breast cancer | Both | MDA-MB-231 | HUVECs | STIM1 promotes angiogenesis by reducing exosomal miR-145 which targets IRS1 | Pro-angiogenesis | [40] |
| NA | Breast cancer | *In-vitro* | MCF-7 and MM-231 | ADSCs | SMAD pathway | Pro-angiogenesis | [41] |
| miR-135b | Multiple myeloma | Both | RPMI8226, KMS-11 and U266 | ECs | Suppression of FIH-1 | Pro-angiogenesis | [42] |

| Exosomal cargo | Tumor type | Type of study (*in-vitro/ in-vivo*) | Cell lines | Target cell | Mechanisms | Function | References |
|---|---|---|---|---|---|---|---|
| Angiogenin, bFGF, VEGF | Multiple myeloma | Both | ST33MMVT and RPMI8226 | ECs, bone marrow stromal cells | Activation of P53, N-terminal kinase, C-jun and STAT3, | Pro-angiogenesis | [43] |
| miR-9 | Melanoma | *Both* | SK23 | ECs | JAK-STAT pathway | Pro-angiogenesis | [44] |
| IL-6, VEGF, and MMP-2 | Melanoma | *In-vitro* | HTB63, Mewo, and A375 | ECs | WNT5A signaling pathway | Pro-angiogenesis | [45] |
| GM-CSF, HIF-1α, HIF-2α | Melanoma | *Ex-vivo* | NA | ECs and M1/M2 macrophages | Upregulation of VEGF expression | Pro-angiogenesis | [46] |
| Tetraspanin Tspan8 (D6.1A) | Pancreatic cancer | Both | BSp73AS | ECs | Upregulation in the expression of MMP, VEGF, and VEGFR | Pro-angiogenesis | [47, 48] |
| Wnt4 | Colorectal cancer | Both | HT29 and HCT116 | ECs | Wnt/β-catenin pathway | Pro-angiogenesis | [49] |
| lncRNA UCA1 | Pancreatic cancer | *In-vitro* | PANC-1, MIA PaCa-2, BxPC-3, Aspc-1, Sw1990, and HEK293T | HUVECs | AMOTL2/ERK1/2 Signaling Pathway | Pro-angiogenesis | [50] |
| M-phase-related transcripts | Colorectal cancer | *In-vitro* | SW480 | ECs | Modulation of M-phase of cell cycle and activation of cell proliferation | Initiate angiogenesis | [51] |
| miR-21 | Lung cancer | *In-vitro* | SV40 | HUVECs | Upregulation of VEGF | Pro-angiogenesis | [52] |
| miR-23a | Lung cancer | *In-vitro* | NCI-H1437, H1648, H1792 and H2087 | HUVECs | Exosomal miR-23a increased angiogenesis and vascular permeability by targeting prolyl hydroxylase and tight junction protein ZO-1 | Pro-angiogenesis | [53] |
| miR-141 | Small cell lung cancer | *In-vitro* | H446 and H1048 | HUVECs | Exosomal miR-141/KLF12 pathway | Pro-angiogenesis | [54] |
| Profilin 2 | Small cell lung cancer | *In-vitro* | H446 | HUVECs | t PFN2 activated Smad2/3 in H446 and pERK in ECs | Pro-angiogenesis | [55] |
| Vasorin | Hepatocellular carcinoma | *In vitro* | HepG2 | HUVEC | Promote cell proliferation and migration | Pro-angiogenesis | [56] |
| Angiopoietin-2 | Hepatocellular carcinoma | Both | Hep3B, SNU182, SNU387, Li7 and MHCC97H | HUVECs | Tie2-independent pathway | Pro-angiogenesis | [57] |
| miR-1290 | Hepatocellular Carcinoma | *In-vitro* | Hep3 B and HepG2 | HUVECs | miR-1290-Induced proangiogenic phenotype via targeting SMEK1 | Pro-angiogenesis | [58] |
| NA | Renal cancer | *In-vitro* | 786-0 | HUVEC | Upregulation of VEGF, expression and downregulation of hepaCAM | Pro-angiogenesis | [59] |
| NA | Renal cancer | *In-vitro* | 786-0 | 786-0 | Increase in the expression of CXCR4 and MMP-9 | Enhance migration and invasion | [60] |
| CA9 | Renal cancer | *In-vitro* | 786-0 | HUVEC | Increasing the MMP-2 expression | Pro-angiogenesis | [61] |

| Exosomal cargo | Tumor type | Type of study (*in-vitro/ in-vivo*) | Cell lines | Target cell | Mechanisms | Function | References |
|---|---|---|---|---|---|---|---|
| miR-549a | Renal cancer | Both | 786-0 and 293T | HUVECs | Exosomal miR-549a affects angiogenesis and endothelial cell migration by silencing HIF1α in HUVECs | Pro-angiogenesis | [62] |
| miR-27a | Renal clear cell carcinoma | *In-vitro* | 786-0, RPTEC and HEK293T | HUVECs | RCCC-derived miR-27a-loaded exosomes inhibit SFRP1 expression and accelerate tumor angiogenesis in RCCC | Pro-angiogenesis | [63] |
| EDIL-3 | Bladder cancer | *In-vitro* | TCC-SUP, T24, and SV-HUC | HUVEC | Promote cell proliferation and migration | Pro-angiogenesis | [24] |
| miR-181a | Papillary thyroid cancer (PTC) | Both | BCPAP and K1 | HUVECs | Hypoxic PTC-secreted exosomes delivered miR-181a that inhibits DACT2 via downregulating MLL3, leading to YAP-VEGF-mediated angiogenesis | Pro-angiogenesis | [64] |
| miR-21 | Head and neck squamous cell carcinoma | Both | FaDu | $CD14^+$ human monocytes | Increasing the expression of M2 polarization markers of TAMs | Pro-angiogenesis | [65] |
| ICAM-1, CD44v5 | Nasopharyngeal carcinoma | *In-vitro* | C666-1, NP69 and NP460 | HUVEC | Src kinase, ERK1/2 kinase, p38 MAPK, RhoA/ROCK, and eNOS | Pro-angiogenesis | [66] |
| PFKFB-3 | Nasopharyngeal carcinoma | *In-vitro* | CNE2 | HUVEC | Increasing in the production of Fru-2,6-P2 and lactate | Pro-angiogenesis | [67] |
| HMGB3 | Nasopharyngeal carcinoma | Both | CNE1, CNE2, 5-8 F, 6-10B and NP69 | HUVECs | HMGB3-containing nEXOs accelerated angiogenesis in vitro and in vivo | Pro-angiogenesis | [68] |
| FAM225A lncRNA | Esophageal squamous cell carcinoma cells | *In-vitro* | ECA109, TE-1, KYSE150, and KYSE-410, and HET-1A | HUVECs | Sponging miR-206 thus derepressing its targets NETO2 and FOXP1 thereby activating PI3K/Akt/NF-κB/Snail axis | Pro-angiogenesis | [69] |
| miR-130a | Gastric cancer | Both | SGC-7901 | HUVEC | Downregulation of c-MYB | Pro-angiogenesis | [70] |
| NA | Chronic myeloid leukemia | Both | K562 | HUVEC | Src pathway | Pro-angiogenesis | [71] |
| IL-8 | Chronic myeloid leukemia | Both | LAMA84 | HUVEC | MAPK signaling | Pro-angiogenesis | [72] |
| miR-92a | Chronic myeloid leukemia | *In-vitro* | K562 | ECs | Targeting integrin-α5 | Pro-angiogenesis | [73] |
| miR-210 | Chronic myeloid leukemia | *In-vitro* | K562 | ECs | Downregulation of EFNA3 | Pro-angiogenesis | [74] |
| miR-21 | Chronic myeloid leukemia | Both | K562 LAMA84 | HUVEC | Downregulation of RhoB | Anti-angiogenesis | [75] |
| TGF-β | Prostate cancer | *In-vitro* | LNCAP, DU145, and PC3 | Fibroblasts | SMAD-dependent signaling | Pro-angiogenesis and pro-tumorigenesis | [76] |

| Exosomal cargo | Tumor type | Type of study (*in-vitro/ in-vivo*) | Cell lines | Target cell | Mechanisms | Function | References |
|---|---|---|---|---|---|---|---|
| C-Src, IGF-IR, FAK | Prostate cancer | *In-vitro* | DU145, PC3 and C4-2B | ECs | Upregulation of VEGF | Pro-angiogenesis | [77] |
| VEGF | Ovarian cancer | *In-vitro* | CABAI | HUVEC | Acts through its tyrosine kinase receptors | Pro-angiogenesis | [78] |
| CD147 | Ovarian cancer | *In-vitro* | CABAI, A2780, OVCAR3 and SKOV3 | HUVEC | Upregulation of MMP and VEGF | Pro-angiogenesis | [79] |
| ATF2, MTA1, SARS, ROCK1/2 | Ovarian cancer | *In-vitro* | CAOV3 | HUVEC | Upregulation of VEGF and HIF-1α | Pro-angiogenesis | [80] |
| miR-221-3p | Cervical cancer | *In-vitro* | CasKi, SiHa, HeLa and SW756 | MVECs | CC cells-derived exosomes harboring miR-221-3p enhanced MVEC angiogenesis in CC by decreasing MAPK10 | Pro-angiogenesis | [81] |
| miR-141-3p | Ovarian cancer | *In-vitro* | SKOV-3a | HUVECs | Activating the JAK/STAT3 and NF-κB signaling pathways | Pro-angiogenesis | [82] |
| PTCH 1, SMO, SHH, Ihh | Cervical cancer | *In-vitro* | SiHa, HeLa and C33a | HUVECs | CC cells-derived exosomes promote pro-angiogenic response in endothelial cells via upregulation of Hh-GLI signaling and modulate downstream angiogenesis-related target genes | Pro-angiogenesis | [83, 84] |
| TIE2 | Cervical cancer | *In-vitro* | SiHa, HeLa and THP1 | HUVECs | TIE2-high tumor cells deliver TIE2 to macrophages to induce TIE2-expressing macrophages via exosomes | Pro-angiogenesis | [85] |
| RAMP2-AS1 lncRNA | Chondrosarcoma cells | *In-vitro* | SW1353 | HUVECs | Sponging miR-2355-5p thus derepressing its target VEGFR2 thereby increasing angiogenic cell surface receptors | Pro-angiogenesis | [86] |
| miR-92a-3p | Retinoblastoma | Both | WERI-Rb1 | HUVECs | Exosomally delivered miR-92a-3p modulates angiogenesis by targeting KLF2 | Pro-angiogenesis | [87] |
| miR-155 | Burkitt's lymphoma | *In-vitro* | Raji | ARPE-19 | Upregulation of VEGF-A expression via VHL/HIF-1α pathway | Pro-angiogenesis | [88] |

***Abbreviations:*** *AnxA2: annexin A2; ATF2: alcohol acetyltransferase II; BMSCs: bone marrow stromal cells; bFGF: basic fibroblast growth factor; bFGFR: basic fibroblast growth factor receptor; CXCR4: C-X-C chemokine receptor type 4; CA9: carbonic anhydrase 9; DLL4: delta-like 4; ECs: endothelial cells; EVs: extracellular vesicles; ESCRT: endosomal sorting complex for transport; EGFR/MAPK: epidermal growth factor receptor/mitogen-activated protein kinase; ERRFI1: ERBB receptor feedback inhibitor 1; eNOS: endothelial nitric oxide synthase; EFNA3: ephrin-A3; EGFRVIII: epidermal growth factor receptor VIII; FIH-1: factor inhibiting HIF-1; FOXP1: forkhead box protein P1; FAK: focal adhesion kinase; GM-CSF: granulocyte-macrophage colony stimulating factor; HUVECs: human umbilical vein endothelial cells; HBMVECs: human brain microvascular endothelial cells; HCC: hepatocellular carcinoma; HNC: head and neck cancer; HIF-1: hypoxia-inducible factor-1; HOXD10: homeobox Protein Hox-D10; HIF1α: hypoxia-inducible factor-1α; HMGB3: high mobility group protein B3; IRS1: insulin receptor substrate 1; IL-8: interleukin 8; ICAM-1: intercellular adhesion molecule 1; IGF-IR: insulin-like growth factor-I receptor; Ihh: Indian hedgehog homolog; JAK-STAT: Janus tyrosine kinase-signal transducer and activator of transcription; KLF4: Krueppel-like factor 4; KLF12: Krueppel-like factor 12; lncRNAs: long non-coding RNAs; MVEs: multivesicular endosomes; MVBs: multivesicular bodies; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; MTA1: metastasis-associated protein 1; NPC: nasopharyngeal carcinoma; nEXOs: nuclear exosomes; PTC: papillary thyroid cancer; PUFA: polyunsaturated omega-3 fatty acid; PI3K: phosphoinositide 3-kinases; PKM: M2-pyruvate kinase; PFN2: profilin-2; PI3K/Akt/NF-κB: phosphoinositide 3-kinases/Akt/nuclear factor-κB; PDGF: platelet derived growth factor; PFKFB-3: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PTCH 1: protein patched homolog 1; RCC: renal cell carcinoma; RCCC: renal clear cell carcinoma; RhoA/ROCK: Ras homolog family member A/Rho-associated kinase; ROCK1/2: Rho-associated kinase ½; SCLC: small cell lung cancer; siRNAs: small interfering RNAs; STIM1; stromal-interacting molecule 1; STAT3: signal transducer and activator of transcription 3; SMEK1: suppressor of MEK protein; SFRP1: secreted frizzled-related protein 1; SARS: severe acute respiratory syndrome; SMO: smoothened; SHH: sonic hedgehog; TEX: tumor-derived exosomes; TME: tumor microenvironment; tPA: tissue plasminogen activator; TGF-β: transforming growth factor β; VEGFA: vascular endothelial growth factor A; VEGFR: vascular endothelial growth factor receptor; VHL/HIF-1α: Von Hippel-Lindau/hypoxia inducible factor-1α; YAP-VEGF: yes-associated protein-vascular endothelial growth factor; ZO-1: zona occludens 1.*

**Table 1.**
*Tumor derived exosomes as carrier of pro-angiogenic cargo from different cancer models promotes neo-angiogenesis.*

### 3.1 Glioblastoma

Exosomes derived from glioblastoma cells are known to carry different mRNAs, miRNAs and angiogenic factors which interacts with ECs and thus stimulate angiogenesis. Kucharzewska et al. demonstrated export of pro-angiogenic factors IL-8 and PDGF through exosomes derived from the hypoxic glioma cells and thus induce endothelial proliferation and cell migration by activating the PI3K/AKT signaling pathway [30]. Exosomes from glioblastoma cells showed enrichment of different non-coding RNAs that include, microRNAs (miRNAs): miR-148a-3p, miR-182-5p; long non-coding RNAs (lncRNAs): POU3F3, HOTAIR, CCAT2 in the regulation of glioma cell angiogenesis [22, 28, 29, 32, 33]. Exosomes derived from glioma cells are also known to carry pro-angiogenic proteins such as EGFRvIII, VEGF-A and DII4 which are important for tumor growth, survival and angiogenesis through the activation of Akt and MAPK signaling pathways [25–27, 31].

### 3.2 Breast cancer

Breast cancer derived-exosomes transfer majorly pro-angiogenic microRNAs: miR-10b, miR-101, miR-105, miR-122, miR-145, miR-210 and miR-373 responsible for tumor invasion, metastasis and lead to angiogenesis [34–36, 39–41]. However, Wu et al. found that exosomes secreted from breast cancer cells loaded with miR-497 are responsible for anti-angiogenesis by downregulating the VEGF and HIF-1 [37]. Maji et al. have observed that Annexin A2 was transferred via breast cancer exosomes to ECs and induces the process of vascularization and angiogenesis through the tissue plasminogen activator (tPA)-dependent manner *in-vitro* and *in-vivo* [38].

### 3.3 Multiple-myeloma

Multiple myeloid cancer cells derived exosomes are known to carry miR-135b and responsible for tube formation in ECs by suppressing its target FIH-1 [42]. Wang et al. observed that various pro-angiogenic factors are released into the exosomes derived from multiple myeloma cells such as angiogenin, bFGF and VEGF that promote tumor growth [43].

### 3.4 Melanoma

In a study conducted by Zhuang et al. demonstrated that exogenous miR-9 can advance tumor angiogenesis by downregulating the SOCS-5 levels, which can discordantly regulate the JAK-STAT signaling pathway [44]. Hood et al. have observed exosomes released from melanoma cells stimulate the expression of HIF-1α, HIF-2α and GM-CSF, which leads to angiogenesis in endothelial cells [46]. Moreover, Ekstrom et al. showed that the WNT5A signaling promotes the exosomal secretion from melanoma cells containing immunomodulatory and pro-angiogenic factors such as IL-6, MMP-2 and VEGF [45].

### 3.5 Pancreatic cancer

Pancreatic adenocarcinoma produced exosomes having high levels of tetraspanin Tspan8 (D6.1A) that promote migration, proliferation and sprouting in ECs. Moreover, these exosomes also help in maturation of endothelial progenitor cells [47, 48].

Guo et al. showed that lncRNA UCA1 was exported through exosomes derived from the hypoxic pancreatic cancer cells are responsible for angiogenesis via miR-96-5p/AMOTL2 signaling pathway [50].

### 3.6 Colorectal cancer

Studying the exosomes from the colorectal carcinoma demonstrated that these exosomes carry pro-angiogenic factors Wnt 4, which helps in angiogenesis of ECs through Wnt/β-catenin pathway [49]. Hong et al. found that the exosomes released from SW480 colorectal cancer cell lines are loaded with M-phase related transcripts such as RAD21, CDK8, and ERH and regulate M-phase of the cell cycle and promotes proliferation and in turn enhance angiogenesis [51].

### 3.7 Lung cancer

Exosomes derived from small cell lung cancer (SCLC) cells are found to be enriched with miR-21 and miR-23a, which is correlated with the pro-angiogenic activities in ECs [52, 53]. A study of Mao et al. demonstrated that exosomes from SCLC cells are responsible for pro-angiogenic effect via miR-141/KLF12 pathway in targeted ECs [54]. In another recent study, Profilin2 protein was transferred from the lung cancer cells via exosomes and leads to angiogenesis by activating the t-PFN2 dependent pERK pathway in endothelial cells [55].

### 3.8 Hepatocellular carcinoma (HCC)

Vasorin (VASN), a type I transmembrane protein has an effective role in tumor progression and angiogenesis, was secreted by exosomes of hepatocellular carcinoma cells (HCC) and promotes the migration of HUVEC cells [56]. In another study of Xie et al. showed that angiopoietin-2 protein is transferred to ECs from HCC cells via exosomes and responsible for pro-angiogenesis [57]. Recently, it was found that miR-1290 is also released from the HCC cells through exosomes and responsible for angiogenesis by inducing the miR-1290 induced pro-angiogenic phenotype in endothelial cells, by targeting the SMEK1 [58].

### 3.9 Renal cell carcinoma (RCC)

Zhang et al. demonstrated that exosomes derived from renal cancer cell enhances angiogenesis by upregulating the expression of VEGF and downregulating the hepaCAM expression in ECs [59]. Moreover, exosomes derived from renal cancer 786-0 cells promotes invasion and migration of the endothelial cells through upregulation of chemokine receptors CXCR4 and MMP-9 [60]. A recent study of Hou et al. observed that the exosomes derived from renal clear cell carcinoma (RCCC) are loaded with miR-27a and inhibits SFRP1 expression which leads to accelerated angiogenesis in HUVECs [63].

### 3.10 Bladder cancer

Beckham et al. observed that the exosomes derived from urine of patients with bladder cancer and high-grade bladder cancer cell lines contain an angiogenic factor. Epidermal growth factor (EGF)-like repeats and discoidin I-like domain-3 (EDIL-3)

that facilitate cell proliferation and migration which leads to angiogenesis in endothelial cells. EDIL-3 activated EGFR signaling overrule this EDIL-3 induced bladder cell migration [24].

### 3.11 Papillary thyroid cancer (PTC)

In a recent study by Wang et al. observed that miR-181a is delivered by hypoxic PTC-secreted exosomes inhibits DACT2 by downregulating MLL3, leading to YAP-VEGF-mediated angiogenesis by increasing proliferation and forming capillary-like network in HUVECs. Further, angiogenic potential of hypoxic PTC-secreted exosomes was confirmed in-vivo, which was reversed in presence of hypoxic miR-181 inhibitor [64].

### 3.12 Head and neck cancer (HNC)

Chan et al. showed that nasopharyngeal carcinoma (NPC) derived exosomes are supplemented with pro-angiogenic factors, ICAM-1 and CD44v5, which helps in angiogenesis of endothelial cells [66]. In another study by Gu et al. recognized a vital role of PFKFB-3 in NPC derived exosomes, which helps in migration, proliferation and angiogenesis of HUVECs [67]. Exosomes derived from FaDu cells are highly enriched with miR-21, captured by monocytes present in the TME and responsible for increasing the expression of M2 polarization of TAMs markers, which helps in tumor progression by regulating the tumor invasiveness and angiogenesis [65]. In a recent study, it was observed that a nuclear protein HMGB3 is transferred to endothelial cells via exosomes released from NPC cells and responsible for accelerated angiogenesis *in-vitro* and *in-vivo* [68].

### 3.13 Esophageal squamous cell carcinoma (OSCC)

Zhang et al. demonstrated that exosomes released from esophageal squamous cells are enriched with lncRNA FAM225A, which accelerates esophageal squamous cell carcinoma progression and angiogenesis by sponging miR-206. Further, they showed the upregulation of NETO2 and FOXP1 expression when FAM225A absorbed the miR-206 thereby activating PI3K/Akt/NF-κB/Snail axis [69].

### 3.14 Gastric cancer

Exosomes derived from gastric cancer cell are enriched with miR-130a and plays a central role in tumor angiogenesis. They showed that exosomal miR-130a is able to facilitate angiogenesis by downregulating the c-MYB, which is an important transcription factor in different biological processes [70]. In another study by Li et al. demonstrated that exosomes released from irradiated gastric cancer cells promote invasiveness and proliferation of endothelial cells [89].

### 3.15 Chronic myeloid leukemia (CML)

LAMA84 a human CML cell line releases exosomes and are able to trigger diverse signaling pathways in ECs, leading to enhanced expression of important angiogenic

factor IL-8 [72]. Umezu et al. observed that exosomes from leukemia cells can transport miR-92a into ECs and responsible for enhanced tube formation and migration by downregulation of integrin-$\alpha_5$ [73]. In another study, it was found that leukemia cell derived exosomes are able to induce tube formation in HUVECs by activating Src [71]. It has been observed that exosomes released from K562 leukemia cells are loaded with miR-210 downregulate the receptor tyrosine kinase ligand, Ephrin A3 (EFNA3) [74]. However, in contrast, Taverna et al. showed that curcumin treatment deeply changes the molecular properties of exosomes released by leukemia cells, in particular, deplete the exosomes of the pro-angiogenic proteins and leads to enrichment of proteins with anti-angiogenic activity and miR-21 [75].

### 3.16 Prostate cancer

Exosomes derived from prostate cancer cells are known to carry TGF-β1 protein, which can induce the differentiation of recipient fibroblasts to myofibroblasts [76]. In a study by DeRita et al., showed that prostate cancer cell exosomes were loaded with, IGF-IR, FAK and c-src, which could promote tumor angiogenesis [77].

### 3.17 Ovarian cancer

Taraboletti et al. demonstrated that exosomes from ovarian cancer cells are known to carry pro-angiogenic growth factor VEGF, which helps in interaction between tumor and endothelial cells and is very important for angiogenesis [78]. Ovarian cancer exosomes are enriched with pro-angiogenic protein CD147, ATF 2, MTA1, SARS and ROCK1/2. They observed that these proteins can enhance the expression of vital angiogenic factors like VEGF, HIF-1α and MMPs and resulting in the enhanced angiogenesis of HUVECs [79, 80]. Additionally, Masoumi-Dehghi et al. observed that exosomes from ovarian cancer cells are enriched in miR141-3p, which helps in angiogenesis by activating the JAK/STAT and NF-kB signaling pathways [82].

### 3.18 Chondrosarcoma

Cheng et al. demonstrated that microarray analysis revealed that exosomes released from chondrosarcoma cells carried lncRNA RAMP2-AS1, which promotes HUVECs migration, proliferation, and tube formation which leads to angiogenesis through miR-2355-5p/VEGFR2 axis, thereby regulating the angiogenic ability of endothelial cells. Successive experiments showed that RAMP2-AS1 knockdown could decrease the pro-angiogenic effect of exosomes released from chondrosarcoma cells [86].

### 3.19 Retinoblastoma

Recently a study conducted by Chen et al. demonstrated that exosomes released by human retinoblastoma cell line WERI-Rb1, were enriched inmiR-92a-3p. The study, predicted that Krüppel-like factor 2 (KLF2) might activate target of miR-92a-3p, using bioinformatics tools & analysis. Thus, exosomal miR-92a-3p was found to modulate tumor angiogenesis by targeting KLF2 [87].

### 3.20 Burkitt's lymphoma

A study performed by Yoon et al. observed that miR-155 is transported from EBV-positive Burkitt's lymphoma cells derived exosomes which could induces angiogenesis in retinal epithelial pigment (RPE) cells (ARPE-19) by upregulation of transcriptional and translational levels of VEGF A via VHL/HIF-1α pathway. Thus, study demonstrated that miR-155 accumulation through exosomes affect nearby recipient cells [88].

### 3.21 Cervical cancer

Zhang et al. observed that exosomes released from cervical cancer cells harboring miR-221-3p, which accelerate the MVEC migration, proliferation, invasion and angiogenesis in cervical cancer cells by regulating MAPK10 [81]. In another study performed by Bhat et al. showed that cervical cancer exosomes were highly enriched with upstream proteins of hedgehog-GLI signaling includes, PTCH1, SMO, SHH and Ihh [83]. Also, they observed that these cervical cancer exosomes facilitate pro-angiogenic endothelial reconditioning through transfer of Hedgehog-GLI signaling components [84].

## 4. Therapeutic potential of tumor-exosomes in angiogenesis

The discovery of exosomes as natural carriers of different mRNAs, miRNAs and lncRNAs makes them a suitable candidate as therapeutic drug vehicles and drug carriers to target cancer cells and modulation of tumor microenvironment. Recent advance in the field reveals several success stories (**Table 2**). The manipulation of

| Exosomal cargos | Study models | Study Outcome | References |
|---|---|---|---|
| let-7a miR | Breast cancer | Secreted exosomes delivered miR-let7a to the breast cancer cells expressing EGFR and inhibited cancer growth by blocking angiogenesis | [90] |
| HGF siRNA | Gastric cancer | Exosomes decrease the tumor growth and angiogenesis in gastric cancer by delivering hepatocyte growth factor siRNA (HGF siRNA) | [91] |
| Antisense RNA targeted to miR-150 | NA | Downregulated the expression levels of VEGF in mice and blocked angiogenesis | [92] |
| miR-21, miR-23b, miR-27a/b, miR-320b, let-7 and let-7a | Breast cancer | DHA treated exosomes have altered miRNA content that have anti-angiogenic properties in breast cancer | [93] |
| miR-340 | Old Bone Marrow Stromal Cells (BMSCs) | Exosomes having miR-340, inhibits angiogenesis through HGF/c-MET signaling pathway in ECs | [94] |
| miR-21 | Chronic Myeloid Leukemia (CML) | Exosomes transferred miR-21 to ECs and downregulated the expression of RhoB | [75] |

***Abbreviations:*** *HGF: hepatocyte growth factor; EGFR: epidermal growth factor receptor; VEGF: vascular endothelial growth factor; DHA: docosahexaenoic acid; RhoB: Ras homolog family member B.*

**Table 2.**
*Engineered exosomes as anti-angiogenic drug carriers in different cancer models.*

exosomes as drug carriers provides significant advantage for example their nonimmunogenic nature [95]. Exosomes are also known to carry different cell surface molecules due to which they have a commendable ability to transgress numerous biological barriers, such as the BBB (blood-brain barrier). They are highly stable in blood, which permits them to perform long distance intercellular communication [96]. Clinical data from various studies revealed that progression of cancer can be delayed or prevented when tumor angiogenesis is blocked [97]. So, angiogenesis during tumor development has now become the major emphasis of study and angiogenesis inhibition is evolving as a new method to treat cancer [98]. Recent investigations reported that exosomes can decrease or increase angiogenesis based on their molecular content. Thus, there is a lot of promise in developing engineered exosomes to transport numerous biological and synthetic genetic materials that can modify the expression of various genes involved in tumor angiogenesis [99]. For example, Ohno et al. demonstrated that modified exosomes carrying EGF or GE11 on their surface can deliver miR let-7a (tumor suppressor miR) to EGFR expressing breast cancer cells in RAG2−/− mice model. Their previous investigation showed that GE11-exosomes which delivered miR-let 7a, effectively downregulated HMGA2 expression in cancer cells [90]. This study verifies that exosomes can be used as drug delivery vehicle to transport their cargo efficiently to the target cells. Exosomes have capability to act as carriers for delivering different small interfering RNAs (siRNAs) for targeted cancer treatment. Exosomes having HGF siRNA packed inside them can be transported into gastric cancer cells, where they downregulate the HGF expression [91]. Liu et al. demonstrated that exosomes are able to transport antisense RNA targeted to miR-150, which induces the expression of VEGF. They established that the neutralization of miR-150 downregulates the VEGF levels in mice and blocked angiogenesis [92]. Gupta et al. have shown that the bone marrow stromal cells (BMSCs) are involved in the tumor progression by secreting different pro-angiogenic factors, bFGF and VEGF [100]. In another study, it was observed that the miR content of exosomes derived from old and young BMSCs was different from each other. Young BMSC exosomes were highly enriched with miR-340, which inhibited the angiogenesis through HGF/c-MET signaling pathway in ECs. The antiangiogenic effect of older BMSCs was remarkably enhanced, when miR-340 was transferred to older BMSC exosomes that was highly expressed in young BMSC exosomes. Therefore, this investigation indicates the exosome-based cancer therapy via replenishment of miRNAs of exosomes [94]. The Arg-Gly-Asp (RGD) sequence containing peptide specifically bounds to αVβ3 integrin and plays an important role in endothelial cell survival, migration and angiogenic growth. In a study performed by Wang et al. showed successful binding of the RGD sequence containing peptide to the exosomal membrane surface and thereby binding of the αVβ3 integrin on the surface of angiogenic blood vessel. Thus, engineered exosomes are emerging as a new probable therapeutic motor for angiogenesis therapy [99]. In another study, it has been observed that curcumin treated CML cells released the exosomes, which are highly enriched with miR-21, which is further transferred to ECs and downregulates the expression of RhoB [75]. Docosahexaenoic acid (DHA) is a polyunsaturated omega-3 fatty acid (PUFA) and popularly known for its anti-cancer and anti-angiogenesis properties. A group of researchers demonstrated that exosomes released from the DHA-treated breast cancer cell lines are highly enriched with miRs, including miR-21, miR-27a/b, miR-23b, miR-320b, let-7 and let-7a, which are well known for their anti-angiogenic properties. They observed the increased expression of these miRs when exosomes were co-

incubated with the endothelial cells. Collectively, the exosomes show a strong therapeutic potential as natural nano carrier [93].

## 5. Conclusion

Herein, we have emphasized the current advances in the roles of tumor derived exosomes in cancers of different origins in tumor angiogenesis. Exosomes could modulate the angiogenic programming in target cells by transferring the angiogenic cargoes that include different mRNAs, miRNAs, lncRNAs and proteins. Angiogenesis is a very complex process in which aberrant growth of tumor and its metastasis occurs. So, the inhibition of angiogenesis is a pivotal point to control the progression of cancer. In spite of increasing amount of information about tumor derived exosomal cargo and changes prompted by them on target cells, the complexity of exosomal cargoes remains to be fully elucidated. There are several limitations and road blockers in the significance of exosomes in cancer therapy. These specifically pertain to exosomal yield, exosomes efficacy and specificity of targeting for effective cancer therapy. This field is yet elusive to assess the effect of exosomes on tumor angiogenesis and use them as potential means for different cancer therapies. So, future investigations should focus on identifying the fundamental exosomal cargoes and the mechanisms behind differential loading of different bioactive molecules, whose role could be implemented for designing non-invasive procedures to detect exosomes for cancer diagnosis and prognosis as well as development of effective therapeutic approaches based on exosomes.

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## Conflicts of interest

The authors declare that there are no competing/conflicts of interest.

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