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The molecular conversations of sarcomas: exosomal non-coding RNAs in tumor's biology and their translational prospects

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Abstract
Exosomes mediate cell-to-cell crosstalk involving a variety of biomolecules through an intricate signaling network. In recent years, the pivotal role of exosomes and their non-coding RNAs cargo in the development and progression of several cancer types clearly emerged. In particular, tumor bulk and its microenvironment co-evolve through cellular communications where these nanosized extracellular vesicles are among the most relevant actors. Knowledge about the cellular, and molecular mechanisms involved in these communications will pave the way for novel exosome-based delivery of therapeutic RNAs as well as innovative prognostic/diagnostic tools. Despite the valuable therapeutic potential and clinical relevance of exosomes, their role on sarcoma has been vaguely reported because the rarity and high heterogeneity of this type of cancer. Here, we dissected the scientific literature to unravel the multifaceted role of exosomal non-coding RNAs as mediator of cell-to-cell communications in the sarcoma subtypes.

Keywords Sarcomas, Exosomes, Non-coding RNAs, Tumor microenvironment, microRNAs, circRNA, LncRNAs

Introduction

Sarcomas are malignant neoplasms that develop in connective tissues, representing about 15% and 1% of all malignant tumors in children and adults respectively [1]. Over 100 sarcoma histological subtypes have been identified, each characterized by distinct clinical course and therapeutic approach [2]. Based on the site of occurrence, sarcomas are also classified in Soft Tissue Sarcomas (STSs) and Primary Bone Sarcomas (PBSs). Among the others, STSs include liposarcoma, synovial sarcoma, Kaposi's sarcoma, and rhabdomyosarcoma. On the other hand, osteosarcoma, Ewing's sarcoma of bone, and chondrosarcoma are defined as PBS [3].

The majority of sarcomas are sporadic with unknown etiology, although several genetic syndromes and/or environmental factors have been found associated with their onset. Among them, radiation therapy [4], extensive

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surgery of the axillary lymph nodes, pathogenic monogenic and polygenic alterations in cancer-associated genes (TP53-related hereditary cancer syndromes, familial adenomatous polyposis, Noonan's syndrome, Rubinstein-Taybi's syndrome, Beckwith-Wiedemann's syndrome, and neurofibromatosis type 1) have been counted [5]. Moreover, the complex dynamic interactions between sarcoma cells and immune cells of the tumor microenvironment (TME) are involved in adaptation to changing environmental conditions and providing a higher chemoresistance potential. Therefore, a deeper look at tumor microenvironment and the need to identify the vehicles of tumor cells-TME cross-talk prompted researcher to focus on exosomes' role. Among the molecules shuttled by exosomes, non-coding RNAs (ncRNAs) are gaining particular attention for their ability to fine-tune gene expression in recipient cells, acting as either tumor suppressors or oncogenes, which make them promising therapeutic cargo. In this scenario, the application of precision medicine strategies and the discovery of new molecules could prove particularly useful [5–8].

Here, we provide an up-to-date overview of knowledge about sarcoma-derived exosomes focusing on their ncRNAs cargo and their impact on TME, with a look on potential clinical implications including their use as possible therapeutic targets/agents. To our knowledge, this represents the widest and complete overview about the role of exosomal ncRNA in the different subtypes of this cancer.

Overview of exosomes

Exosomes are small extracellular vesicles (EVs) released by a wide range of cells types [9, 10]. EVs serve as a means of intercellular communication, delivering bioactive cargos to target cells to influence their function, and phenotype [11, 12]. Based on their biogenesis and characteristics, exosomes represent a distinct entity from other EVs subtypes (ectosomes, microvesicles, membrane vesicles, and apoptotic bodies) [13–16]. In particular, exosomes have a size lower than 200 nm and their lipid bilayer membrane consists of cholesterol, sphingomyelin, ceramides, phosphatidylcholine, and proteins (e.g. CD9, CD63, and CD81). The small cytosol, devoid of cellular organelles, contains different kind of molecules such as: nucleic acids (coding and non-coding RNAs; single- and double-stranded DNA) and cytoplasmic proteins (e.g. Hsp70, Hsp90) [12]. Exosomes originate by the endosomal pathway through the formation of intraluminal vesicles (ILVs) and then multivesicular bodies (MVBs), which can either fuse with lysosomes for degradation or with the cell membrane to be released in the extracellular environment [12, 14, 17, 18]. This process is regulated by the endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways [12, 19].

ESCRT-dependent exosomes biogenesis, the most investigated pathway, consists of four subcomplexes (ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III) interacting in a specific order [17]. ESCRT-0 is responsible for loading in a ubiquitin-dependent manner, ESCRT-I and ESCRT-II induce bud formation, ESCRT-III drives vesicle pinch-off. Each ESCRT complex requires specific auxiliary proteins to explicit their functions (e.g. VPS4 and ALIX) [17, 20]. ILVs fate towards lysosomal degradation depends on ubiquitination state of cargo proteins and on de-ubiquitinating activity of DUB enzymes. Conversely, the release of exosomes is mediated by RABGTPase proteins (especially RAB27A, RAB27B, RAB11, RAB35, and RAB7) [21], RAB effector molecules, and other factors such as intracellular calcium levels, p53 expression, microenvironmental pH, and heparanase expression [12]. The last event is the MVBs and cell membrane fusion with the consequent exosomes release, performed by the soluble N-ethyl maleimide (NEM)-sensitive factor attachment protein receptor (SNARE) complex (Fig. 1).

In addition, several Authors described non-canonical ESCRT-dependent exosomes biogenesis pathways, as recently reviewed. Among them Alix and HD-PTP represent two alternative components of ESCRT complex that can capture ILVs cargo [19]. Alix operates in three different manner to recognize cargo: (a) through Syndecan and Syntenin proteins, (b) direct interaction with lysobisphosphatidic acid (LBPA) and tetraspanins, and (c) binding to PAR1 and P2Y1 [22–24]. On the other hand, ubiquitinated cargo bound to ESCRT-0 or –I is included in ILVs through HD-PTP-mediated recruiting of ESCRT-III and VPS4 [25].

On the other hand, ESCRT-independent pathways draw out both on lipids and proteins composition of exosomes' membrane, which resembles that of lipid rafts. The most studied is the neutral sphingomyelinase 2 (nSMase2)-ceramide pathway, in which sphingomyelin to ceramide conversion regulates the sorting of ILVs cargo [26]. Tetraspanins have been also found to mediate sorting of ILVs cargo. Indeed, CD63 is pivotal in ILVs formation and sorting of cargo (such as LMP1, VEGF, and ferritin) in exosomes [27, 28, 29].

Absorption and internalization of exosomes by recipient cells occurs by endocytosis, ligand-receptor interaction, or cell membrane fusion. The molecules associated with the surface of exosomes, such as tetraspanins, glycoproteins, and integrins, determine which cells will accept exosomes [17].

Exosomes can also act by modulating the microenvironment by promoting interactions between tumor and stromal cells. Stromal cells, upon accepting tumor-derived exosomes, generate a pro-tumor

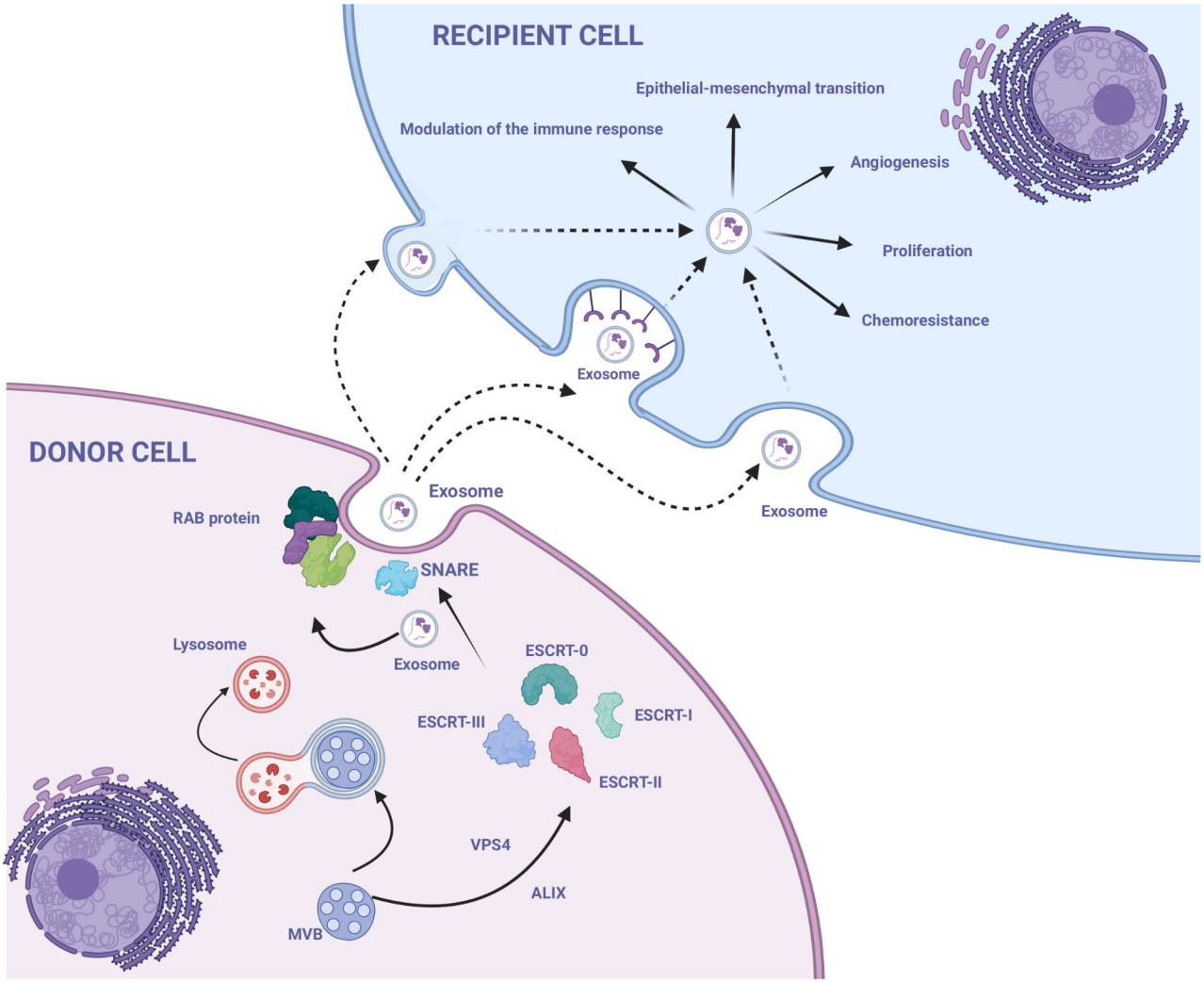

Fig. 1 Biogenesis, release, and uptake of exosomes. Exosomes originated from intraluminal vesicles (ILVs) and then included in multivesicular bodies (MVBs), can fuse with lysosomes and undergo to degradation or with the cell membrane to be released as exosomes into the extracellular space. The exosomes formation is a process mediated by the Endosomal Sorting Complex Required for Transport (ESCRT)-dependent pathway, which consists of four complexes from 0 to III. The release of exosomes is mediated by RABGTPase proteins and the soluble N-ethyl maleimide (NEM)-sensitive factor attachment protein receptor (SNARE) complex, which lead to MBVs and cell membranes fusion and exosome release. Exosomes uptake can be exploited by endocytosis, ligand-receptor interaction, or fusion with cell membrane. Generated with BioRender.com

microenvironment by releasing, in turn, exosomes which promote several biological processes in tumor cells including cell proliferation, invasion, migration as well as epithelial to mesenchymal transition (EMT) [21]. In addition, experimental evidence on exosomes highlighted that tumor cells can transfer their drug resistant phenotype trough the exosomal delivery of multidrug resistance (MDR) transporters, antiapoptotic proteins, pro-survival miRNAs, upregulation of DNA repair genes, and pro-inflammatory cytokines [20].

Overview of non-coding RNAs

Non-coding RNAs can be divided into housekeeping ncRNAs, and regulatory ncRNAs; the first are found stably expressed and to sustain cellular survival (transfer RNA, ribosomal RNA, and small nucleolar RNA). In contrast, regulatory ncRNAs primarily consists of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), with lncRNAs accounting for 80% of ncRNAs. They range from 200 to 100.000 nucleotides in length and perform different functions at multiple levels of gene expression, including epigenetic, transcriptional and post-transcriptional regulation [30]. Among their regulatory functions, lncRNAs interact with cytoplasmic proteins to lengthen or shorten their half-life or bind to mRNAs modulating their translation. LncRNAs are also able to sequester cytoplasmic miRNAs extending their lifespan [31–33].

The miRNAs play essential roles in regulation of several biological processes. [34]. Their synthesis begins in the nucleus, where RNA polymerase II generates

DNA-encoded primary miRNA (pri-miRNA); in the next step, the ribonuclease Drosha transforms the pri-miRNA into the precursor miRNA (pre-miRNA) with a length of 60–70 nt. The final step is the Dicer (RNA ribonuclease III)-mediated cleavage of the pre-miRNA into double-stranded mature miRNA (19–25 nucleotides) in the cytoplasm [35]. They act by binding 3′ untranslated regions (3′UTRs) of mRNAs to post-transcriptionally suppress gene expression, either by translation repression or by mRNA degradation [36]. Those inhibiting tumor-suppressing genes are named oncomiRs and are involved in regulation of several cancer hallmarks [37]. In contrast, other miRNAs act as tumor suppressors; they prevent cancer initiation and progression through downregulation of various oncogenes with a role in proliferation, invasion, and metastasis. These miRNAs were found downregulated in many cancer types, thus restoring their expression through exosomes-mediated delivery emerges as a promising novel therapeutic approach [38].

A singular class of ncRNAs, characterized by a ring structure, are named circular RNAs (circRNAs) [39]; their biogenesis utilizes non-canonical splicing events [40]. In detail, closed circular RNAs are generated mainly by back-splicing from pre-mRNA, where the 5′ end is ligated to the 3′ end in a reverse direction [41] (Fig. 2).

Stable and abundant, they can have a long lifespan because resistant to exonucleases digestion [42, 43]. Based on the retained pre-mRNA sequence, circRNAs

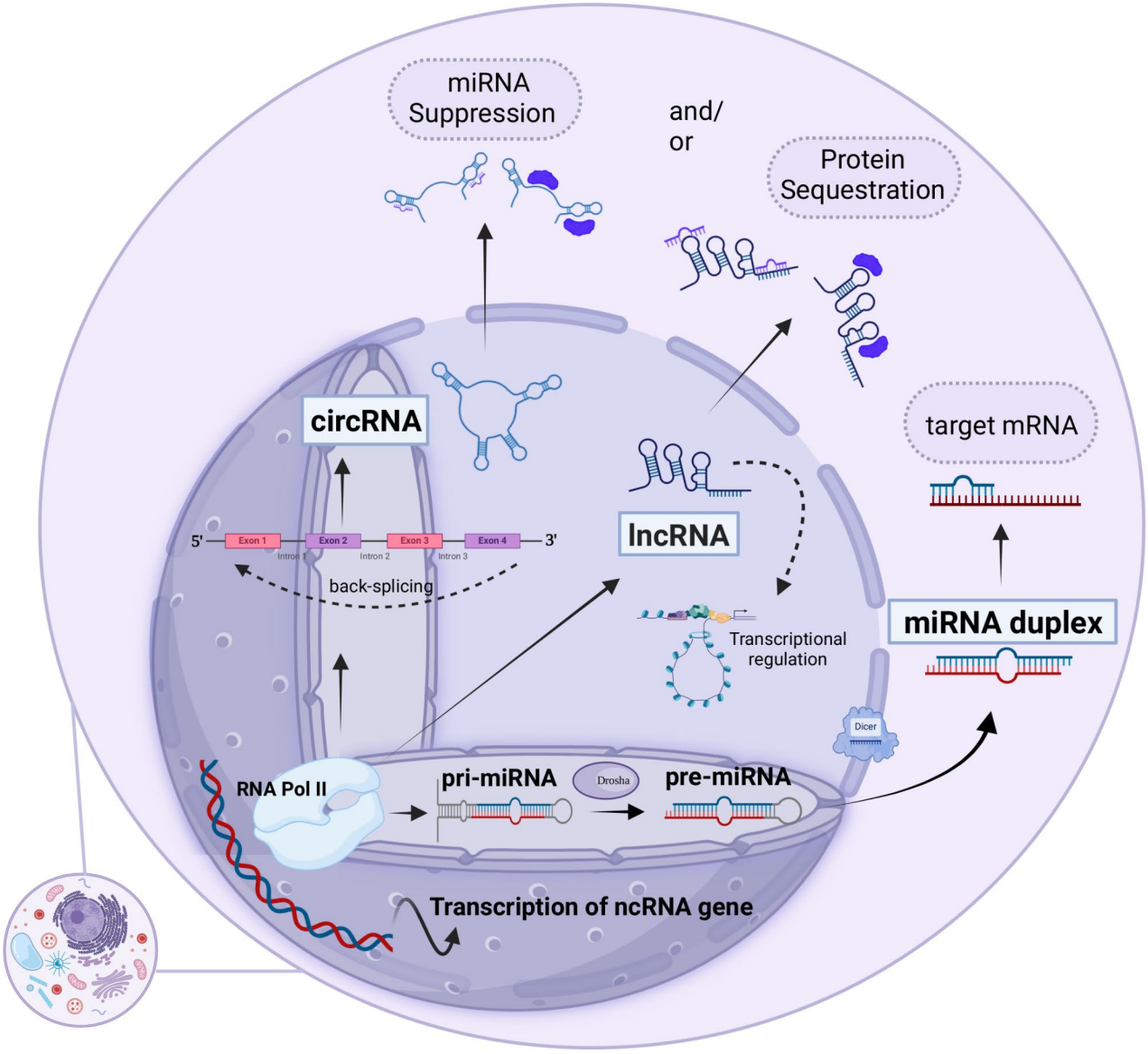

Fig. 2 Biogenesis and functions of ncRNAs.> The biogenesis mechanisms and the main biological process perturbed by microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs) are depicted. Generated with BioRender.com

can be categorized into three primary types: exonic circRNAs (ecircRNAs), intronic circRNAs (ciRNAs) and exon-intron circRNAs (EIcircRNAs) [44]. Accumulating evidence shows that circRNAs are ubiquitously distributed in eukaryotic cells [45], where they perform important and multiple biological functions such as gene expression regulation, microRNA sponging, RNA-binding Proteins (RBPs) regulation, and even encoding of functional peptides [46]. Several studies have shown that circRNAs are aberrantly expressed in various diseases, especially cancer [47, 48]; indeed, dysregulation of circRNA expression is considered to be one of the main mechanisms driving tumorigenesis and progression [49]. They can influence cancer growth by controlling important signaling pathways involved in cell differentiation, proliferation, EMT, metastasis, and cell death [50]. Some circRNAs, by modulating the AKT1/mTOR axis, can modify metabolism and autophagy, facilitating tumor spread through exosomal communication [51]. Overall, due to their distinctive functional properties, they are also considered potential therapeutic targets as well as diagnostic and prognostic biomarkers.

The ncRNAs also mediate the epitranscriptomic alterations regulating expression at chromosomal level [52]. In particular, among other functions, lncRNAs can control the structure of chromatin by binding directly to enzymes that modify it or by taking part in multiprotein complexes known as "chromatin modification complexes", which act by adding or removing methyl/acetyl groups or ubiquitin groups to nucleosomal histones. Moreover, lncRNAs themselves are epigenetically regulated, since their promoters have been found to be hypo- or hypermethylated in several cancer types [53]. Similarly, miRNAs can be silenced by hypermethylation, but they also regulate epigenetic modulators, including histone acetyltransferases (HATs), DNA methyltransferases (DNMT), and chromatin remodeling enzymes [53].

Overview of tumor microenvironment

The TME consists of blood vessels, extracellular matrix (ECM), fibroblasts, immune cells, bone marrow-derived inflammatory cells, and signaling molecules [54] (Fig. 3).

It is of critical importance, since several evidence suggest that the malignant behavior of cancer is not attributable only to tumor cells but also to the composition of their TME [55, 56].

Indeed, the cross-talk between tumor cells and the tumor microenvironment plays a very important role in the initiation, progression, metastasis, and drug resistance of cancer [57]. Tumor-derived exosomes contain EMT-inducing molecules (e.g. TGF-β, HIF1α, β-catenin, IL-6, caveolin-1) that promote the loss of E-Cadherin and

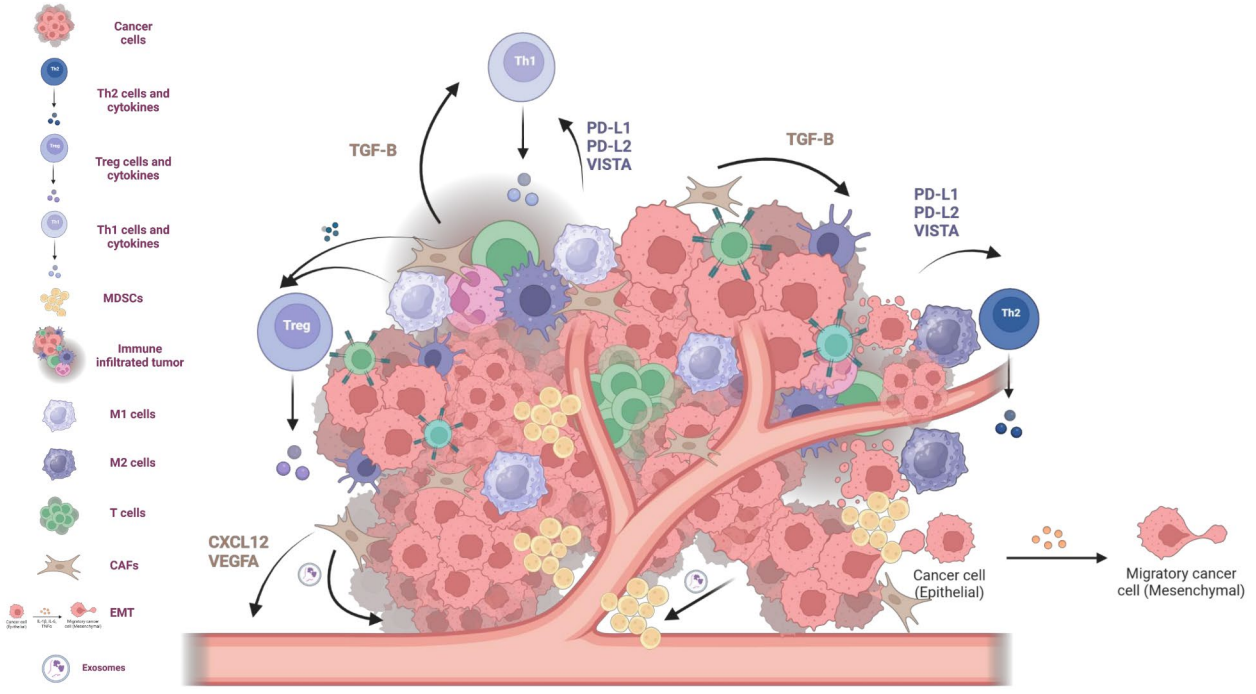

Fig. 3 Tumor microenvironment (TME) complexity depiction. Tumor-associated macrophages (TAMs) can have an M1 or M2 phenotype with opposite effects on anti-tumor immune surveillance. PD-L1, PD-L2 and VISTA can directly suppress T cell activity by recruiting regulatory T cells (T-reg). Cancer-associated fibroblasts (CAF) by secreting cytokines and resistance factors-loaded exosomes influence function of immune cells and can contribute chemotherapy and radiotherapy resistance. Myeloid-derived suppressor cells (MDSCs) have a strong immunosuppressive activity. Exosomes are also released by tumor cells self-enhancing proliferation, migration and immune escape. Generated with BioRender.com

cell polarity, and the gain of N-cadherin, Twist, Snail, and Vimentin [17]. Primary tumors also release exosomes to establish pre-metastatic niches by remodeling distant tissues, generating a favorable environment for tumor cells colonization. Release of angiogenesis-promoting exosomes by tumor cells, acting on endothelial cells, has been also described under hypoxic conditions [21, 58]. The main actors that stimulate angiogenesis found in tumor-derived exosomes include Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF), Platelet-Derived Growth Factor (PDGF), basic Fibroblast Growth Factor (bFGF), Transforming Growth Factor β (TGF-β), Tumor Necrosis Factor α (TNF-α), and Interleukin 8 (IL-8) [17]. Moreover, cancer cells impact the immune system by guiding the recruitment and differentiation of immune cells that infiltrate the tumor. The most prominent immune cells in the TME are macrophages, which are derived from peripheral blood monocytes and are defined as tumor-associated macrophages (TAMs) [54, 59]. TAMs can have an M1 anti-tumor phenotype and an M2 pro-tumor phenotype [59]. M1-like TAMs are involved in Th1-type immune responses and are the predominant force in innate host defense and tumor cell killing, while M2-like TAMs activate Th2-type immune responses and have a crucial role in facilitate EMT and angiogenesis [59–61]. TAMs show remarkable plasticity within the TME because, under specific conditions, they are able to switch from one phenotype to another. TAMs are responsible for the suppression of adaptive anti-tumor immunity. Indeed, they express high levels of immune checkpoint ligands such as PD-L1, PD-L2 and VISTA, which can directly suppress T cell activity. Furthermore, they recruit regulatory T cells (T-reg) that also favor the suppression of T cell immunity [57].

Cancer-associated fibroblasts (CAFs), with different subpopulations, represent another fundamental component of the TME [62]. It has been observed that CAFs interact with tumors, promoting proliferation, angiogenesis and shaping the immunosuppressive microenvironment to escape immune surveillance [63, 64]. Furthermore, they can modulate the metabolism of tumor cells through the secretion of exosomes whose content can suppress mitochondrial function, accelerate glycolysis and thus improve proliferation [65, 66]. Preclinical studies have found that the immunosuppressive role of CAFs is attributable to the secretion of TGF-β, which influences the function of various cell types, such as T cells, macrophages, and neutrophils. Moreover, it has been observed that they favor disease progression through the secretion of CXCL12 [54], and VEGFA which promote angiogenesis [62, 67]. CAFs can also contribute to chemotherapy and radiotherapy resistance by secreting cytokines and providing exosomes loaded with drug resistance factors to tumor cells [63].

A critical cell population also found in the tumor microenvironment is represented by myeloid-derived suppressor cells (MDSCs) [68], immature myeloid cells that have strong immunosuppressive activity [69]. MDSCs originate in the bone marrow and, in individuals with cancer, migrate to peripheral lymphoid organs and tumor bulk, where they contribute to the generation of the TME. MDSCs are able to inhibit the immune response through the production of suppressive molecules that act directly by inhibiting the anti-tumor response mediated by effector T cells or by inducing regulatory T cells. Moreover, exosomes released by tumor cells are able to facilitate the activation and expansion of these cells, which enhance cancer cells proliferation, migration and immune escape [69].

The role of exosomal ncRNA in sarcomas: the cross-talk between tumor cells and TME

As for other cancers, sarcoma-derived exosomes are enriched with miRNAs, lncRNAs, and circRNAs, which are more abundant in sarcoma cells than in normal cells. Numerous studies found that their levels have a clinicopathological relevance. Indeed, it has been observed that greater expression of these exosomal contents in patients' tissues and sera are associated with higher rates of metastasis and relapse, as well as shorter survival time [21, 70–73]. The malignant behavior of sarcomas is also attributable to TME, whose composition varies based on tumor subtype, anatomical location, age, sex, genomic complexity, and treatment [74]. Exosomes mediate cellular communications between sarcoma and TME cells, and are critical players in sarcomagenesis by influencing tumor progression and metastasis [21, 75–78]. The development of sarcoma is mainly linked to the immune microenvironment and in particular to TAMs, which are crucial in shaping the local response of TME to tumor by both enhancing and inhibiting the immune defense against sarcoma [21].

Despite promising discoveries in this field, clinical application of exosomes is still challenging likely due to the rarity of these tumors and the limited literature about this topic. A comprehensive review of existing knowledge can guide future investigations on "neglected" sarcoma subtypes. To this aim, PubMed database was searched to gather all available articles on exosomal ncRNAs and their involvement in the development and progression of sarcoma, with a focus on their impact on TME. The query was built as follows: (sarcoma subtype) AND (exosomes) AND ((miRNA) OR (circRNA) OR (lncRNA) OR (piwiRNA) OR (snRNA) OR (snoRNA)). All ncRNAs and their biological implications were summarized in Table 1; Fig. 4.

Table 1 Most relevant ncRNAs and their functions in the different subtypes of sarcoma

Sarcoma type	Exosomal ncRNA	Function	Reference
Osteosarcoma	miR-21	Regulation of anti-tumor immune response, promotion of metastasis and angiogenesis	[80]
	miR-148a	Stimulation of endothelial cells to secrete angiogenic factors and to organize into tube-like structures	[81]
	miR-21-5p	Stimulation of endothelial cells to secrete angiogenic factors and to organize into tube-like structures	[81]
	miR-21-5p	Promotion of proliferation and invasion of OS cells	[82]
	circ-LMO7	Sponging of miR-21-5p and suppress the proliferation of OS cells	[83]
	miR-25-3p	Oncosuppressor by inhibiting SOX4	[75]
	miR-25-3p	Promotion of capillary formation and invasion	[75]
	miR-144-3p	Decrease the viability of OS cells	[84]
	miR-486-3p	Inhibition of progression	[85]
	has-miR-23a-3p	Promotion of progression	[86]
	miR-15a	Inhibition of proliferation and invasion	[87]
	miR-501-3p	Modulation of osteoclastogenesis	[88]
	let-7a	Enhancement of invasion and migration	[89]
	miR-221-3p	Growth and metastasis of OS cells, modulating SOCS3/JAK2/STAT3 axis	[90]
	miR-181a-5p	Polarization of macrophages to M2 phenotype	[91]
	miR-1228	Modulation of migration and invasion of OS cells by downregulating the expression of SCAI protein	[92]
	lncRNA SNHG17	Promotion of proliferation and metastasis	[70]
	miR-1307	Promotion of proliferation, migration and invasion of OS cells by reducing AGAP1protein expression	[93]
	miR-675	Promotion of invasion and migration of non-cancer fibroblasts; putative biomarkers	[94]
	miR-331-3p	Conferring chemoresistance	[96]
	hsa-circ-103,801	Association with shorter survival time of patients and transfer of chemoresistance	[71]
	circ_0056285	Potential diagnostic biomarker	[97]
	lncRNA CASC15	Potential diagnostic biomarker	[78]
	lncRNA PVT1	Promotion of OS cell proliferation and migration	[98]
	lncRNA XIST	Promotion of growth and metastasis	[99]
	miR-206	Inhibition of tumor progression	[100]
	miR-208a	Enhancement of progression	[101]
	miR-199a-5p	Inhibition of growth and angiogenesis	[104]
	linc00852	Enhancement of proliferation, migration, and invasion	[105]
	lncRNA OIP5-AS1	Enhancement of autophagy	[106]
	lncRNA ANCR	Association with adryamicin resistance	[107]
	lncRNA LIFR-AS1	Promotion of proliferation and invasion of OS cells by interacting with the miR-29a/NFIA axis	[108]
	linc00881	Promotion of tumor cell migration to lung; secretion of pro-inflammatory cytokines	[109]
	linc00662	Activation of M2 macrophage phenotype; promotion of EMT and metastasis	[110]
	lncRNA ELFN1-AS1	Polarization of M2 macrophage and promotion of progression	[111]
Chondrosarcoma	lncRNA RAMP2-AS1	Competitive binding with miR-2355-5p, positive regulating of proliferation, tube proliferation of human umbilical vein endothelial cells through up-regulation of VEGFR-2	[112]
Ewing's sarcoma	miR-210	Inhibition of apoptosis through reduction of CASP8AP2 levels	[114]
	LINC00847	Inhibition of proliferation, migration and invasion of ES cells.	[117]

Table 1 (continued)

Sarcoma type	Exosomal ncRNA	Function	Reference
Kaposi's sarcoma	miR-210	Promotion of growth under hypoxic condition	[122]
	miR-K12-9	Regulation of IRAK1 and MYD88 weakening inflammation	[121]
	miR-k12-5	Regulation of IRAK1 and MYD88 weakening inflammation	[121]
	miR-17-92 cluster	Oncogenic Function	[123]
	miR-106b/25 cluster	Oncogenic Function	[123]
Rhabdomyosarcoma	miR-1246	Promotion of tumor-associated fibroblasts proliferation and local invasion, migration and metastasis	[127, 133]
	miR-1268	Promotion of tumor-associated fibroblasts proliferation and local invasion, migration and metastasis	[127, 133]
	miR-486-5p	Enhancement of proliferation, migration, and invasion in fibroblasts; putative biomarker	[134]
Liposarcoma	miR-25-3p	Correlated with the development and progression of DDLPS	[144]
	miR-92-a-3p	Correlated with the development and progression of DDLPS	[144]
Synovial Sarcoma	miR-92b-3p	Potential non-invasive biomarker of SS	[77]

DDLPS: Dedifferentiated liposarcoma; EMT: epithelial-to-mesenchymal transition; ES: Ewing's sarcoma; OS: Osteosarcoma; RMS: Rhabdomyosarcoma; SS: Synovial sarcoma

Osteosarcoma

Osteosarcoma (OS), although rare, represents the most common bone cancer affecting children and adolescents (from 5 to 20 years old) and adults in their seventies. It is characterized by high rate of lung metastases and mortality. In OS pathogenesis, the most important altered pathways include Wnt, Notch, NF-KB, p53, PI3K/AKT and MAPK. Several exosomal miRNAs have been found to participate in the osteosarcoma pathogenesis by targeting key genes in these pathways [79]. OS-derived exosomes carrying miR-21 regulate the tumor's immune response, promote tumor metastasis and angiogenesis [80]. Exosomes carrying miR-148a and miR-21-5p stimulate endothelial cells to secrete angiogenic factors and their organization into tube-like structures [81]. Moreover, miR-21-5p from MSCs-derived exosomes by suppressing PIK3R1 expression activates PI3K/Akt/mTOR pathway and promotes proliferation and invasion in OS cells [82]. The oncogenic role of miR-21-5p is supported also by the recent work by Luo et al. [83], in which Authors demonstrated that circ-LMO7 binds miR-21-5p reducing its activity. Interestingly, this circRNA was also found downregulated in exosomes from OS cell line. The miR-25-3p has intracellular and extracellular oncogenic functions in OS, as at the intracellular level it affects the expression of SOX4 in bone tissue acting as cancer suppressor. On the other hand, exosomal miR-25-3p is able to promote capillary formation and invasion throughout vascular endothelial cells [75]. Jiang et al. observed that exosomes carrying miR-144-3p decrease the viability of OS cells, as high levels of this miRNA are associated with a lower tendency to migration and invasion. The expression of miR-144-3p is negatively correlated with the expression of ZEB1, a transcription factor that promotes EMT [84]. Exosomal miR-486-3p by sponging the circKEAP1/MARCH1 axis was found to inhibit progression of OS [85]. Yang et al. identified hsa-miR-23a-3p as key differentially expressed miRNA in IDO1 overexpressing OS cells and found an association with OS progression [86]. Wu et al. identified miR-15a as a major cargo of serum-derived exosomes, which when internalized by OS cells in vitro suppressed the GATA2/MDM2 axis, inhibiting proliferation and invasiveness [87]. Influence on bone loss was found for OS-derived exosomal miR-501-3p, which modulate osteoclastogenesis via PTEN/PI3K/Akt signaling pathway [88]. Precursor miRNA let-7a level was upregulated in TAMs-derived exosomes and was found to enhance invasion and migration OS cells by blocking C15orf41 [89]. The miR-221-3p carried by M2-TAM-derived exosomes has been observed to be involved in the growth and metastasis of OS cells. Up-regulation of miR-221-3p modulates the SOCS3/JAK2/STAT3 axis by downregulating SOCS3 expression [90]. OS cells-derived exosomal miR-181a-5p induce polarization of M2

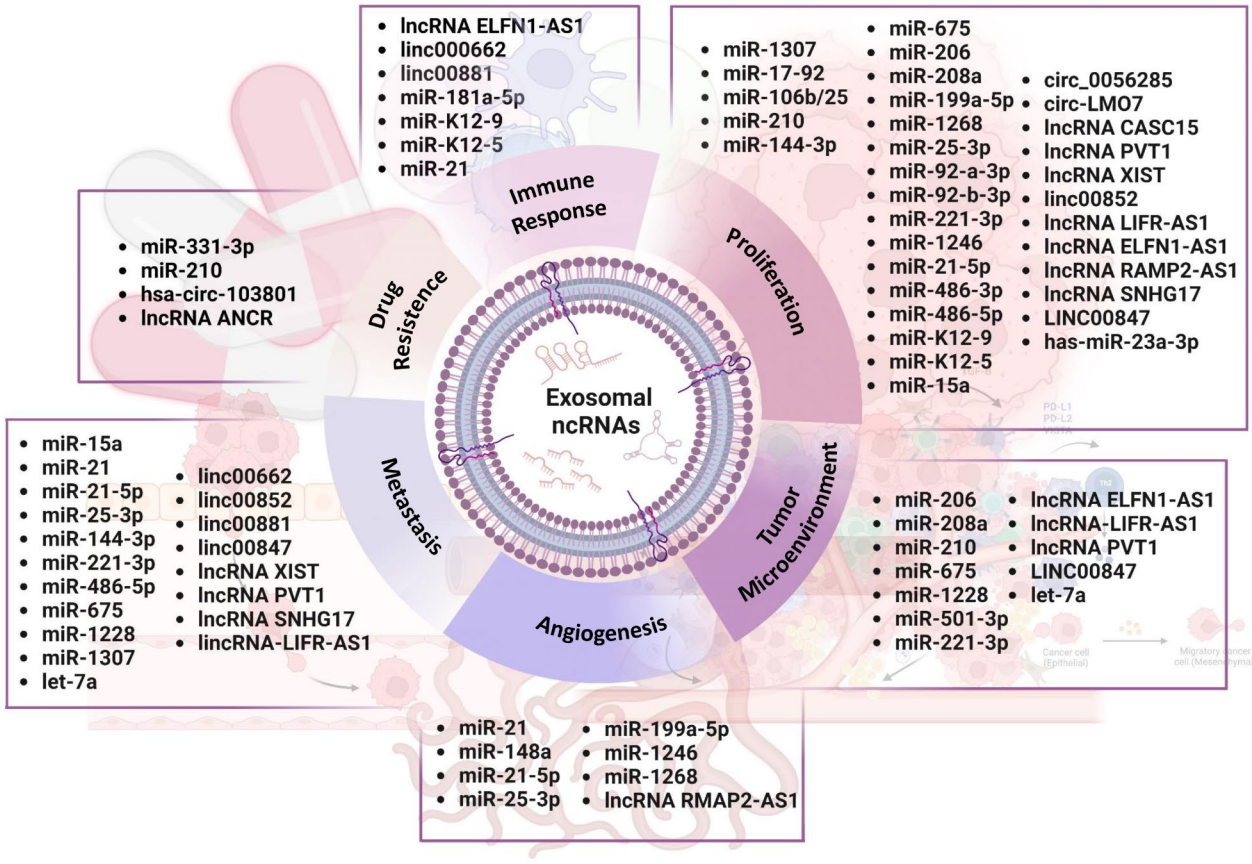

Fig. 4 Summary of ncRNA enriched in sarcoma-derived exosomes and their function. Relevance of each ncRNA in the different sarcoma subtypes are exploited in the text below and in Table 1. Generated with BioRender.com

macrophages via targeting RORA [91]. Exosomal miR-1228 transferred from CAFs to OS cells is able to modulate their migration and invasion by downregulating the expression of SCAI protein, an important mediator that controls these biological processes [92]. An essential exosomal cargo of OS-related CAFs is the lncRNA SNHG17 that by interacting with miR-2861 favor proliferation and metastasis of OS [70].

Exosomal miR-1307 promotes the proliferation, migration and invasion of osteosarcoma cells by reducing the expression of the Arf1 GTPase-activating (AGAP1) protein involved in endolysosomal trafficking [93]. miR-675 was found to influence invasion and migration of non-malignant fibroblasts and to be high in metastatic OS, thus serving as a putative biomarker [94]. Kerri Wolf-Dennen et al. observed that metastatic OS cells induce an immunosuppressive tumor microenvironment through the secretion of exosomes. In particular, the TAMs uptake of exosomes from metastatic OS cells leads to decreased phagocytosis, efferocytosis, and macrophage-mediated cell killing due to increased IL-10, TGF-β_2, and CCL22 mRNA levels, which are cytokines associated with M2 macrophages phenotype [95]. Meng et al. demonstrated that exosomes carrying miR-331-3p derived from chemoresistant OS cells confer resistance to sensitive ones [96]. Pan et al. observed that hsa-circ-103,801 is upregulated in the serum exosomes of patients with OS and it was associated with shorter survival time than patients with low levels of hsa-circ-103,801. They also observed that exosomal hsa-circ-103,801 derived from cisplatin-resistant cells enhances the resistance of OS cells to this drug [71]. Huo and Dou found that circ_0056285 was highly expressed in serum of OS and proved its potential diagnostic value [97]. Similarly, lncRNA CASC15 was found up-regulated in plasma from OS patients as compared with control subjects [78]. It was reported by Zhao et al. that the exosomal lncRNA PVT1, secreted by bone marrow mesenchymal stem cells (BMSCs), promotes OS cells proliferation and migration through degradation inhibition and expression increase of ERG protein [98]. BMSCs through exosome transfer to OS cells the X-inactive specific transcript (XIST), a long non-coding RNA, which bind and down-regulates miR-655 level leading to ACLY up-regulation. This up-regulation determines an increase in lipid deposition and β-catenin activity that promotes growth and metastasis of OS [99].

BMSC-derived exosomal miR-206 uptake by OS cells was found to inhibit tumor progression by targeting TRA2B [100]. Qin et al. reported that BMSC-derived exosomal miR-208a enhances the progression of OS cells *via* the down-regulation of PDCD4 and activation of the ERK1/2 pathway [101]. In sarcoma tumor microenvironment, BMSCs mediate intercellular communications through exosomes, promoting the invasion and metastasis of OS cells [102].

BMSCs can be recruited and educated by sarcoma-derived exosomes to undergo differentiation resulting in a tumor-promoting phenotype. For example, OS-derived exosomes can induce LINE-1 hypomethylation leading to epigenetic transformation of MSCs into a pro-tumorigenic and pro-metastatic phenotype of CAFs [21, 103]. They promote sarcoma progression and the formation of metastatic niches through matrix remodeling and through exosome-mediated communications established with sarcoma cells. Furthermore, MSC-derived exosomes help to evade the inhibitory signals of hypoxia and chemotherapeutic agents favoring survival and proliferation of sarcoma cells [21]. At the same time, exosomes from sarcoma cells are able to release miRNAs into endothelial cells, increasing the expression levels of angiogenic factors including VEGFA, IL-6 and IL-8, triggering angiogenesis [21, 81]. Conversely, miR-199a-5p by targeting VEGFA inhibits the growth and angiogenesis of osteosarcoma [104]. Proliferation, migration, and invasion of OS cells were found to be enhanced by AXL-associated exosomal linc00852 [105]. Exosomal lncRNA OIP5-AS1 through down-regulation of miR-153 enhances ATG5 expression and hence cell autophagy [106]. LncRNA ANCR has been indicated as a critical mediator of resistance to adryamicin, tumor progression and survival in OS [107]. Zhang et al. shown that exosomal lncRNA LIFR-AS1 derived from TAMs can promote proliferation and invasion of OS cells by interacting with the miR-29a/NFIA axis [108]. Chang et al. highlighted the crosstalk between OS cells and lung fibroblasts mediated by exosomal linc00881, which favor tumor cells migration to lung. In particular, they found that linc00881, by sponging miR-29c-3p, activates NF-κB signaling in lung fibroblast, which results in upregulation of MMP2. In addition, a secretion of pro-inflammatory cytokines was observed [109]. Exosomes loaded with linc00662, released by PITX1 knockdown OS cell lines, were able to activate M2 macrophages in cell co-culture assays. Activated M2 macrophages secreted CCL22 that promoted EMT and metastasis in OS [110]. Wang and colleagues demonstrated that OS cells-derived exosomal lncRNA ELFN1-AS1, by sponging miR-138-5p and miR-1291, induces M2 macrophage polarization facilitating OS progression [111].

Chondrosarcoma

Chondrosarcoma is a rare malignant tumor that affects adults between the ages 40 and 60. It commonly targets the axial bones and the proximal ends of the limbs, such as humerus and proximal femur. Cheng at al. observed that the levels of lncRNA RAMP2-AS1 are higher both in T2 vs. T1 stage and in M1 vs. M0 stage chondrosarcoma patients. Furthermore, high RAMP2-AS1 levels was associated with poor survival. They isolated and identified exosomes derived from chondrosarcoma cells and demonstrated that exosomes containing lncRNA RAMP2-AS1 were internalized by human umbilical vein endothelial cells (HUVECs), enhancing their angiogenic potential through modulation of the miR-2355-5p/VEGFR2 axis [112]. In particular, lcnRNA RAMP2-AS1 primarily acts as a competitive endogenous RNA (ceRNA) with VEGFR-2 mRNA for binding to miR-2355-5p, positively regulating proliferation, tube formation of HUVECs [112, 113].

Ewing's sarcoma

Ewing's sarcoma (ES) is a bone tumor that develops in children and adolescents, for which the chromosomal translocation t(11, 22)(q24,q12) accounts for 85% of cases. This translocation, determines an oncogenic chimeric fusion protein called EWS-FLI1, which acts as a transcriptional activator of downstream target genes expression, leading to key tumorigenesis events of ES [114–116]. A significant enrichment of exosomes loaded with miR-210 was found under HIF-1α mediated hypoxia, miR-210 through reduction of CASP8AP2 levels exerts a pleiotropic antiapoptotic effects on hypoxic cells [114]. Lu Huang et al. investigated the role of exosomal lncRNAs from BMSCs in the pathogenesis of ES. In particular, they observed that exosomal LINC00847 derived from BMSCs inhibits the proliferation, migration and invasion of ES cells and that LINC00847 is down-regulated in ES cells and tissue samples [117]. Moreover, it has been demonstrated that in the escape phase of immunoediting, ES-derived exosomes directly compromise the immune response against tumor by inducing the release of pro-inflammatory cytokines in $CD33^{+}$ myeloid cells and $CD14^{+}$ monocytes, blocking the differentiation of myeloid cells into dendritic cells [118].

Kaposi's sarcoma

Kaposi's sarcoma (KS) is a tumor caused by Human Herpesvirus 8 (HHV8 - also called KS-associated herpesvirus (KSHV)) infection, in presence or not of immune suppression [119]. There are four types of KS: classic, endemic or African, iatrogenic, and epidemic. KS lesions are characterized by macules, papules, and nodules that are prone to bleeding and ulceration [120].

Exosomes secreted from KSHV-infected cells have been observed to promote malignancy and facilitate communications between normal and infected cells. KSHV genome encodes for 25 mature miRNAs derived from 12 pre-miRNAs, which are all found in exosomes. Exosomal miRNAs from infected cells target multiple signaling pathways associated with the pathogenesis of neoplasms such as PI3k/Akt, MAPK and Wnt [121]. Furthermore, they increase the migration capacity of uninfected endothelial cells, leading to angiogenesis through the stabilization of HIF-1α [122]. Infected cells can transfer miRNAs via exosomes to neighboring cells, promoting a metabolic transformation towards aerobic glycolysis in surrounding uninfected cells. It has been observed that miR-210 can be transferred by exosomes into normoxic cells of the tumor microenvironment and can support the growth of hypoxic tumor cells by providing high-energy molecules such as lactate and pyruvate [122]. Finally, it has been found that miRNAs encoded by KSHV inhibit the innate immune response, for example miR-K12-9 and miR-k12-5 regulate IRAK1 and MYD88 that mediate TLR/IL-1R signaling and decrease IL-6 and IL-8 levels thus weakening inflammation [121]. Chugh et al. observed that in addition to KSHV-encoded miRNAs, systemically circulating exosomes from mice bearing telomerase-immortalized human umbilical vein endothelial cells (TIVE) tumor, which express all KSHV latent genes, were significantly enriched with the host oncogenic miR-17-92 and miR-106b/25 clusters as compared to controls [123]. In addition, in a previous study, they also found that at different KS tumor progression stages were associated different host miRNAs [124].

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common STS in children and adolescents, characterized by a high propensity for local invasion and distant metastasis [125]. While is uncommon in adults, it exhibits an annual incidence rate of 4.3 cases per million individuals who are under the age 20. Notably, the majority of cases are observed in children younger than 10 years [126]. Based on the histological features, RMS is classified into four subtypes, of which embryonal (ERMS) and alveolar (ARMS) are the most common [127]. In pediatric and adolescent patients, ERMS constitutes approximately 60% of RMS and is usually associated with localized disease, favorable sites of onset (head and neck, genitourinary, non-bladder/prostate, and bile duct regions), and better prognosis. ARMS, on the other hand, is less frequent (20% of cases) but more aggressive due to less favorable sites of primary onset and higher metastatic potential. RMS, in adults, has a poor prognosis for both histological subtypes with greater propensity to invasiveness and metastasis [126, 128]. Several studies demonstrated that RMS-derived exosomes carry nucleic acids and proteins implicated in tumor growth and metastasis [129–131].

Focusing on ncRNAs cargo, exosomal miRNAs have been demonstrated to play a role in proliferation, migration, and angiogenesis, thereby supporting tumor growth in RMS [132]. In particular, exosomes carrying miR-1246 and miR-1268 were found enriched in RMS cell lines, and to modulate Wnt pathway, EGFR pathway, angiogenesis, and apoptosis [127]. Similarly, Ghayad et al. reported that miR-1246 and miR-1268 were involved in multiple pathways related to tumourigenesis including Wnt, cadherin, and fibroblast growth factor. In this regard, it has been demonstrated that RMS-derived exosomes influence the proliferation of TAMs, which play a crucial role in promoting local invasion, migration, and metastasis [133]. Inducing the upregulation of miR-486-5p enhanced proliferation, migration, invasion and anchorage-independent growth in recipient fibroblasts. This miRNA was also described as potential candidate as serum biomarker for diagnosis, response evaluation and follow-up of patients after treatment. Indeed, miR-486-5p levels have been found to be high in exosomes from pediatric RMS patients [134].

Liposarcoma

Liposarcoma represents the most common malignant tumor among STS and can be conventionally divided into four subtypes [135]: well-differentiated liposarcoma (40–50% of cases), myxoid liposarcoma (20–30%), dedifferentiated liposarcoma (15–20%) and pleomorphic liposarcoma (5–10%) [136]. Typically widespread in adults aged between 40 and 60 years, an higher incidence in male subjects has been reported [137]. Liposarcomas develop predominantly within or between muscles, deep down, and often appear as painless soft tissue masses; only a small percentage, ranging from 10 to 15%, may present with pain [138–143].

Among the main exosomal miRNAs upregulated in liposarcoma patients, and in particular dedifferentiated liposarcoma (DDLPS), have been found miR-25-3p and miR-92a-3p. Exosome-derived miR-25-3p and miR-92-a-3p have recently been shown to correlate with the development and progression of DDLPS. It has been reported that both miR-25–3p and miR-92a-3p are able to stimulate the secretion of the proinflammatory cytokine IL-6 by TAMs in a TLR7/8-dependent manner, resulting in invasion and proliferation of liposarcoma cells promotion [144].

Synovial sarcoma

Synovial sarcoma (SS) is one of the STS most frequently diagnosed in adults [145]. Conventionally, four histological subtypes are identified: biphasic, monophasic fibrous, monophasic epithelial, and poorly differentiated

[146]. Male individuals are predominantly affected, with a peak incidence between the ages 10 and 35 [147, 148]. Although they can potentially arise in any anatomical site, synovial sarcomas are more frequently diagnosed in juxta-articular sites, in the deep soft tissues of the lower and upper limbs. Synovial sarcoma presents as a slow-growing tumor, usually associated with local pain, with an average duration of symptoms between 2 and 4 years [149]. Uotani K et al. reported that exosomes are enriched in bioactive molecules, including miR-92b-3p, whose expression levels may represent a new approach to monitor the dynamics of synovial sarcoma. Indeed, miR-92b-3p was significantly reduced following surgical resection and adjuvant chemotherapy, while it was found to increase during local recurrence and metastasis spreading. Notably, serum levels of this exosomal miRNA were significantly higher in synovial sarcoma patients compared to healthy individuals. This miRNA exhibited robust discriminatory power between SS patients and the other subtypes, also reflecting tumor burden [77].

Enrichment of pathways target by exosomal miRNAs in sarcomas

To provide an overall functional characterization of the sarcoma-derived exosomal ncRNAs reported in Table 1, we employed the miRPath v4.0 online tool and R version 4.4.0 to highlight the main pathways targeted by the cited ncRNAs, in particular miRNAs [150, 151]. We restricted the analysis to this class of ncRNAs since it is the better studied cargo of extracellular vesicles [152] and is known to influence a plethora of biological processes in surrounding and distant cells. The miRNAs list was subjected to the miRNA-centric analysis with both "genes union" and "pathways union" merging methods, setting false discovery rate (FDR) correction and significance level at $p<0.05$. To identify the miRNA-target interactions (MTIs), in miRPath v4.0, we selected the miRTarBase2022 database, which is a collection of experimentally validated MTIs, and miRBase-v22.1 annotations. Moreover, we selected the KEGG pathway database for the functional enrichment and enabled the post-enrichment analysis to evaluate whether target genes were differentially expressed in sarcoma tissue samples relative to the rest of tissues included in the TCGA dataset (one-tail Mann-Witney U test). Following the "genes union" analysis, 143 pathways were found enriched (Suppl. File 1). Among the most significant ($p<0.001$) (Fig. 5A), KEGG pathways analysis revealed that exosomal miRNAs target genes are involved in several cancer-related pathways (e.g. proteoglycans in cancer, mTOR signaling, MAPK signaling, Hippo signaling), cell proliferation and death (e.g. apoptosis, cell cycle, cellular senescence, p53 signaling pathway, signaling pathways regulating pluripotency of stem cells), and microenvironment perturbation (e.g. TGF-beta signaling, focal adhesion, regulation of actin cytoskeleton, adherens junction). An intriguing finding was the enrichment of viral carcinogenesis and virus infections-related pathways, as well as those related to neurodegenerative diseases. A similar picture emerged also using the "pathways union" methods, as depicted in Fig. 5B (Suppl. File 2). In particular, among the analyzed miRNAs, 13 defined four major clusters that are functionally associated with TME remodeling (cancer-related signaling pathways, cell-cell and cell-ECM adhesion). After the post-enrichment analysis, 27 enriched pathways from the "genes union" were differentially expressed in sarcoma tissue samples as compared with all the other cancer tissue samples in the TCGA dataset (Suppl. File 3). Thereafter, we filtered out those with FDR>0.001 and performed an intersection analysis to identify the common differentially expressed genes ($\log_2$ Fold Change (FC) > |1|) targeted by at least one exosomal miRNAs (Fig. 5C). Moreover, among these pathways, we selected those sharing more than two genes and plotted the relative $\log_2$ FC (Fig. 5D). As above, most of them are associated with tumor cell proliferation, survival and interaction between cancer cells and TME. We speculate that the shared down-regulated genes, although still not described, could be additional targets of the exosomal miRNAs cargo worthy of deeper investigation to assess their putative role in shaping sarcomas evolution and their microenvironment. Notably, we found an important down-regulation of TNF and ERBB4 genes that, since it is known their dual role in different type of cancers [153, 154], we may hypothesize their activity as tumor suppressor genes in specific subtypes of sarcoma.

Conclusions and future directions

In recent years, exosomes were found involved in the development, progression and metastasis spreading of cancer by mediating intercellular communications. Moreover, their role in shaping tumor microenvironment and regulating immune response has been deepened [79]. As we summarized, several exosomal ncRNAs are aberrantly expressed in sarcomas, some even with subtype specificity, and were found to be correlated with the development and progression of these neoplasia. We also reviewed the most recent literature about the influence of exosomal ncRNA in TME remodeling, in particular highlighting the bidirectional cross-talk among cancer cells and the different complex network of non-cancer cells, such as CAFs, TAMs, MDSCs, and immune cells. It has been observed that in sarcoma patients, the high amount of exosomes correlates with tumor volume and staging [155, 156]. As consequence, several studies have been carried out to highlight the possibility of using exosomes as diagnostic and/or prognostic biomarkers as well as in treatment follow-up. Interestingly, exosomes also offer

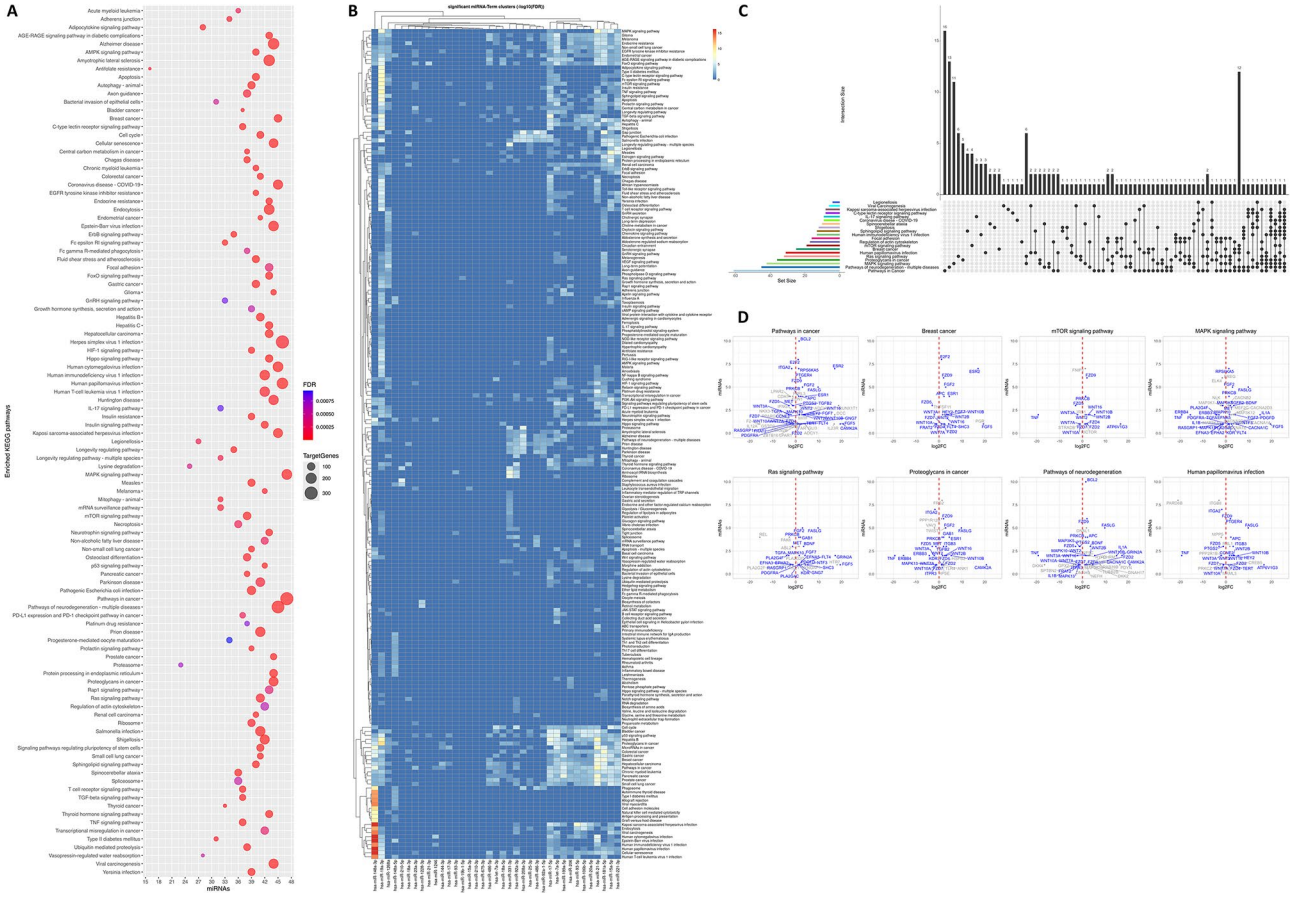

Fig. 5 Pathways enriched by sarcoma-derived exosomal miRNAs. (**A**) Enriched pathways using the genes union method of miRPath v4.0 (FDR < 0.001). (**B**) Pathways enriched using the pathway union method of miRPath v4.0 (FDR < 0.05). (**C**) Intersection analysis of pathways' genes differentially expressed between sarcoma and the remaining tissues samples of TCGA dataset using the post-enrichment analysis of miRPath v4.0. (**D**) Detail of pathways sharing at least 3 differentially expressed genes (blue) targeted by exosomal miRNAs. Genes with log2FC values > |1| and interacting miRNAs > 0 were plotted

a novel approach for precise tumor targeting, potentially impacting both cancer cells and the tumor microenvironment [157, 158]. Exosomes can cross biological barriers easier than other drug delivery nanoparticles [159], holding great promise for delivering RNA-based therapeutics due to their ability to shield RNAs from extracellular degradation [160]. Shimbo et al. employed exosomes to deliver synthetic miR-143 to OS cells leading to inhibition of their migration [161]. Furthermore, modifying exosomes' membrane proteins/peptides through parental cell manipulation or direct engineering after isolation could offer additional advantages for targeted exosome-based RNA delivery [156]. Huang et al. engineered exosomes to improve the delivery of lncRNA MEG3 to osteosarcoma cells both in vitro, and in vivo. In particular, they modified exosomes with the cRGD peptides directed against αvβ3 integrin, which resulted in a more efficient delivery and reduction of proliferation and migration of OS cells [162].

Despite the great potential of exosomes and their ncRNAs cargo, their clinical application remains difficult and challenging mainly hindered by the rarity of sarcomas. This scarcity limits the number of studies, especially for certain subtypes, underscoring the urgent need for collaborative research efforts to bridge the gap.

Abbreviations

ARMS	Alveolar rhabdomyosarcoma
BMSCs	Bone marrow mesenchymal stem cells
CAFs	Cancer-associated fibroblasts
ceRNA	Competitive endogenous RNA
circRNAs	Circular RNAs
DDLPS	Dedifferentiated liposarcoma
ECM	Extracellular matrix
EMT	Epithelial to mesenchymal transition
ERMS	Embryonal rhabdomyosarcoma
ES	Ewing's sarcoma
ESCRT	Endosomal sorting complex required for transport
FDR	False discovery rate
HATs	Histone acetyltransferases
ILVs	Intraluminal vesicles
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated herpesvirus
lncRNAs	Long non-coding RNAs
MVBs	Multivesicular bodies
MDR	Multidrug resistance
MDSCs	Myeloid-derived suppressor cells

miRNAs	Micro RNAs
MSCs	Mesenchymal cells
MTIs	miRNA-target interactions
ncRNAS	Non-coding RNAs
OS	Osteosarcoma
PBSs	Primary Bone Sarcomas
RBPs	RNA-binding proteins
RMS	Rhabdomyosarcoma
SS	Synovial sarcoma
STSs	Soft Tissue Sarcomas
TAMs	Tumor-associated macrophages
TME	Tumor microenvironment

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions

SL and SR designed the work. ML, PL, GC, LCO, MRM, and FC collected data. SR analyzed data. SL and SR interpreted data. ML and PL drafted the work. AMB, GF, SR, and SL substantially revised the work. All authors have approved the manuscript version.

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Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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