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Mini-review

Exosomes in sarcomas: Tiny messengers with broad implications in diagnosis, surveillance, prognosis and treatment

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ABSTRACT

Exosomes are cell-secreted extracellular vesicles, which contain an array of biomolecules, such as proteins, mRNAs, microRNAs, and lipids, take part in intercellular communication and mediate tumor-host interactions. They are increasingly considered as a source of biomarkers for liquid biopsies as well as potential drug vectors. Sarcomas are rare malignant mesenchymal tumours and due to their relative rarity exosomes have not been investigated in as extensively as in epithelial malignancies. Nonetheless, valuable information has been gathered over the last years on the roles of exosomes in sarcomas. In the present review we summarize all relevant data obtained so far from cell lines, animal models and patients with emphasis on their potential clinical utility.

1. Introduction

Sarcomas are a heterogeneous group of solid malignant mesenchymal neoplasms that encompasses more than 50 entities broadly divided into those of the soft tissues and those of the bone [1]. They are rare, accounting for only ~1% of the adult, but up to ~15% of the pediatric cancers [2]. The diagnosis is established on histomorphologic and immunophenotypic grounds complemented, more often than not, by molecular studies thanks to the identification of recurrent genetic alterations in many sarcomas. The mainstay of therapy is complete surgical excision followed by radiation and/or chemotherapy, but promising targeted therapies have also emerged, which inhibit PDGFRα, tyrosine kinases, anaplastic lymphoma kinase (ALK), mTOR, vascular endothelial growth factor (VEGF) or cyclin-dependent kinases [3].

Liquid biopsy is the detection of circulating tumoral elements, which include circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating tumor RNA (ctRNA), tumor-educated platelets and exosomes [4]. Non-invasiveness, representation of tumor heterogeneity and tumor evolution, as well as the ability to repeat easily for the purpose of post-treatment monitoring are considerable theoretical advantages of the liquid biopsy over conventional tissue sampling. In sarcomas, the isolation of CTCs is based either on the size of the circulating cells or on the detection of cell-surface vimentin, since it cannot rely on the detection epithelial cell adhesion molecule (EpCAM), an approach commonly adopted in epithelial cancers [5]. Analysis of sarcoma-derived ctDNA and ctRNA has revealed *EWSR1-FLI1* and *EWSR1-ERG* gene fusions and respective transcripts in Ewing sarcoma, isocitrate dehydrogenase type 1 (IDH1) and IDH2 mutations in chondrosarcoma, chimeric *FUS-CHOP* transcripts in myxoid liposarcoma, as well as miRNA profiles of various sarcomas [5].

Exosomes are lipid-bilayer-enveloped particles measuring 40–120 nm in diameter, which belong to the "extracellular vesicles" along with microvesicles and apoptotic bodies [6]. Exosomes are actively exocytosed and mediate intercellular communication by conveying a variety of biomolecules (proteins, nucleic acids and lipids) to the recipient cells. Physiologically they are implicated in immunity, coagulation, spermatogenesis and central nervous system processes [7]. In cancer they are incriminated in the exploitation of the tumor microenvironment and in the preconditioning of the so called "pre-metastatic niches", remote sites intended to host the metastatic cells [8]. Although the bulk of the available information about the role of exosomes in cancer has been gathered from the more common epithelial tumors, such as breast [9], lung [10] or hepatocellular cancer [11], growing evidence supports that exosomes serve similar functions in sarcomas, too. These include promotion of tumorigenesis, intercellular communication, microenvironment modulation and acquisition of metastatic potential [12,13].

Apart from helping illuminate sarcoma biology, exosomes are emerging biomarkers with valuable diagnostic, prognostic and predictive information, as well as potential therapeutic agents. Here we aim to summarize all relevant evidence obtained hitherto from cell

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Table 1
Potential uses of exosomes by type of sarcoma and sample/material investigated..

	SYNOVIAL SARCOMA	LIPOSARCOMA	KAPOSI'S SARCOMA	GASTROINTESTINAL STROMAL TUMOR (GIST)	EWING SARCOMA	OSTEOSARCOMA	RHABDOMYOSARCOMA	FIBROSARCOMA
DIAGNOSIS AND/OR SURVEILLANCE	carriers of miR-92b-3p [51]	carriers of miR-25-3p and miR-92a-3p [43]	carriers of viral and/or tumoral miRNA signatures [44]	carriers of most of GIST's secretome, which is modified after imatinib treatment [48] and includes diagnostic (KIT, CD34, ANO1/DOG1, PROM1, PRKCQ and ENG) [49] and monitoring markers of durable and/or immediate response to imatinib (SPRY4, SURF4, ALIX, FZD8 and PDE2a) [49]	carriers of *EWSR1-FLI1* [35] and EZH2 [36] mRNA carriers of transcriptional signature including *EWSR1-FLI* [52]	carriers of sets of proteins that are either common or unique among different osteosarcoma cell lines [21] carriers of miR-25-3p [22]	carriers of miR-1246 and miR-1268, a common finding among all five studied rhabdomyosarcoma cell lines [20]	
PROGNOSIS				carriers of proteins with prognostic value (CDKN2A, EPHA4, FHL2, DPP4, EZR, HIF1A and KCTD12) or associated with metastatic disease (SPRY4) [49]		carriers of uPA [23] and miR-675 [24], potential markers of metastatic phenotype carriers of miR-25-3p, a favorable prognostic marker [22]	carriers of distinct miRNA profiles depending on presence or absence of adverse prognostic *PAX-FOXO1* gene fusion [20]	
PREDICTIVE VALUE	carriers of miR-791 associated with resistance to pazopanib [33]					carriers of MDR-1 mRNA implicated in multidrug resistance [27]		
TREATMENT					vectors of miR-34a inducing changes mimicking CD99 silencing [38] boosters of TRAIL efficacy [40]	vectors of miR-143, inhibitor of cell migration [30]	boosters of TRAIL efficacy, but only in combination with flavopiridol [40]	boosters of tumoral antigen immunogenicity [16,17] potential immunoadjuvant agents when enriched with HSP70 [18] vectors of siRNA against RAD51 recombinase [14] boosters of TRAIL efficacy, but only in combination with flavopiridol [40]

INDICATIVE LEVEL OF EVIDENCE COLOR SCALE BY SUBJECT TYPE			
cell lines	animal models	patients (few cases)	patients (small cohorts)

lines, animal models and human patients. In the first part of this review we gather data derived from experimental models and in the second we gather data derived from clinical samples. A concise summary of the reviewed studies is presented in the Table 1 by type of sarcoma, potential clinical application and type of sample or material investigated.

2. Exosomes and sarcoma pathogenesis, diagnosis, surveillance, prognosis and treatment by type of sarcoma: *Data from studies using cell lines and/or animal models*

2.1. Fibrosarcoma

2.1.1. Treatment

Exosomes have been successfully loaded with siRNA against the transcript of the *RAD51* gene, which codes for a recombinase enzyme, and then administered to fibrosarcoma cells of the HT1080 cell line, leading to knockdown of RAD51 recombinase and subsequent massive cell death [14]. Delivery of exosome-free siRNA was equally cytotoxic as the exosomal form in vitro, however, exosomes would be necessary as vectors in vivo due to siRNA's instability in the bloodstream [15].

In terms of immunotherapy, exosomes could contribute in the development of cancer vaccines. Exosomes bearing tumoral antigens, eg fibrosarcoma antigen OVA, help induce and maintain a better anti-tumoral immune response compared to soluble or membrane-bound tumoral antigens, according to murine models of fibrosarcoma using MCA101 cells [16,17]. This response includes strong activation of specific $CD8^+$ and $CD4^+$ T-cells, production of anti-tumoral antibodies and attenuation of immunosuppressive regulatory T-cells (Tregs) in the tumor microenvironment [17].

In another potential immunotherapeutic application, exosomes derived from untreated macrophages and enriched with WEHI-164 cell lysate, HSP70, naloxone, propranolol and/or staphylococcal enterotoxin B exhibited anti-tumoral properties [18]. Most potent was the action of HSP70-treated exosomes, which best stimulated an immune response and caused tumor regression in fibrosarcoma-bearing mice [18].

It should be pointed out that, historically, the term "fibrosarcoma" has described tumors that would now be classified otherwise, since the more recently refined diagnostic criteria exclude neoplasms with an immunohistochemically recognizable line of differentiation or other specific molecular features [19]. Therefore, information gathered from fibrosarcoma cell lines or animal models is not necessarily limited to or representative of what is now perceived as fibrosarcoma, i.e. largely a diagnosis of exclusion.

2.2. Rhabdomyosarcoma

2.2.1. Diagnosis and/or surveillance & prognosis

Ghayad S. et al. identified rhabdomyosarcoma's exosomal miRNA cargo using five different cell lines. On the one hand, they noted a variation in miRNA profiles across the different cell lines, which in large part also reflected the presence of absence of the *PAX-FOXO1* gene fusion, an established adverse prognostic factor [20]. On the other hand, they consistently detected miR-1246 and miR-1268 among all five cell lines [20]. This would justify further evaluation of both exosomal miRNAs as diagnostic and/or prognostic biomarkers in rhabdomyosarcoma.

2.3. Osteosarcoma

2.3.1. Diagnosis and/or surveillance

Proteomic analysis of exosomes and exosomal-free conditioned media from three osteosarcoma cell lines (MG63, SAOS-2, and U2OS) yielded a set of > 3000 proteins mostly implicated in tumor progression (i.e., angiogenesis, cell adhesion and migration) [21]. Proteins that are either common or unique among the studied cell lines were identified, but nevertheless not explicitly specified by the authors [21]. Further evaluation in comparison with normal subjects or other sarcomas could possibly reveal proteomic profiles of diagnostic significance.

Furthermore, miR-25-3p, which in its "free" circulating form has been suggested as a reasonably reliable diagnostic (AUC: 0.868, sensitivity: 71.4%, specificity: 92.3%) but also a potential favorable prognostic marker for osteosarcoma, has been proven detectable in exosomes, too [22], although detection of its exosomal form was not attempted in human plasma.

2.3.2. Prognosis

The conversion of osteosarcoma cells from a non-metastatic to a metastatic phenotype is marked by the activation of the urokinase plasminogen activator (uPA)/uPA receptor (uPAR) axis; metastatic osteosarcoma cells selectively overexpress uPAR, which is stimulated in an autocrine and paracrine fashion by osteosarcoma-produced uPA [23]. The uPA produced by osteosarcoma cell lines is detectable both in a "free" and in an exosome-bound form [23]. Gong et al. suggest that metastatic osteosarcoma cells deliver exosomal miR-675, a regulator of migration-related gene *CALN1*, whereas non-metastatic osteosarcoma cells do not [24]. However, further studies are warranted on whether exosomal uPA or miR-675 can discriminate between osteosarcomas with a metastatic and a non-metastatic potential in human patients.

2.3.3. Predictive value

The treatment of osteosarcoma often suffers from the latter's innate or secondary multidrug resistance [25]. A major resistance mechanism involves the P-glycoprotein (P-gp), an ATP-binding transmembrane transporter coded by the *MDR-1* gene, which pumps chemotherapeutic agents out of the neoplastic cell at an energy cost [26]. Osteosarcoma cell lines made resistant to doxorubicin can induce doxorubicin resistance to susceptible osteosarcoma cells by sharing their *MDR*-1 mRNA via exosomes [27]. Therefore, should exosomal *MDR*-1 mRNA be detectable in the clinical setting, it could possibly function as a predictive biomarker for multidrug resistance.

2.3.4. Treatment

Prompted by the observations that miR-143 is downregulated in osteosarcoma cells [28], promotes apoptosis and suppresses tumorigenicity [29], Shimbo K. et al. showed that transfection of osteosarcoma cells with miR-143 packed either in exosomes or in liposomes diminished their migratory capacity [30]. Compared to liposomes, exosomes transferred smaller amounts of miR-143, but with equivalent antitumoral effects. It is hypothesized that smaller amounts of miR-143 may suffice or that exosomes achieve targeted delivery to key intracellular compartments [30]. Furthermore, exosomes lack synthetic components that liposomes may contain [31], a probable comparative advantage of the former for in vivo applications.

2.4. Synovial sarcoma

2.4.1. Predictive value

Pazopanib, a multitargeted tyrosine kinase inhibitor, is a promising agent against soft tissue sarcoma limited by acquired post-treatment resistance [3]. In synovial sarcoma, the response of the proteome to pazopanib is notable for down-regulation of Wnt-5a and Wnt signaling target frizzled-1 (FZD1) and is traceable in the neoplastic exosomal protein cargo [32]. Shiozawa et al. observed that multiple synovial sarcoma cell lines with acquired resistance to pazopanib shared an overexpression of miR-761, which was postulated to induce chemoresistance by downregulating *TRIP6*, *LMNA* and *SIRT3* genes. miR-761 was successfully detected in extracellular vesicles, which can be considered to be exosomes based on the use of tetraspanins CD9 and CD81 for their isolation [33].

2.5. Ewing sarcoma

2.5.1. Diagnosis and/or surveillance

The fusion of the *EWSR1* gene with an Ets family member gene, most commonly *FLI1*, is the driver molecular event in Ewing sarcoma and therefore an ideal liquid biopsy target candidate [34]. *EWSR1-FLI1* chimeric transcripts have been traced and quantitatively measured in extracellular vesicles from Ewing sarcoma cell lines using an ultrasensitive microwell array which combines mRNA hybridization with digital analysis [35]. Furthermore, data from a 3D Ewing sarcoma tumor model thought to better simulate Ewing sarcoma than monolayer cell line cultures show that tumoral exosomes contain high levels of polycomb histone methyltransferase *EZH2* mRNA [36], which is induced by the *EWSR1-FLI1* chimeric protein and mediates tumor growth and metastasis [37]. The presence of *EZH2* mRNA was confirmed in exosomes isolated from the plasma of seven Ewing sarcoma patients [36].

2.5.2. Treatment

Two of Ewing sarcoma's hallmarks, CD99 expression and the *EWSR1-FLI1* gene fusion, compete with each other in that CD99 maintains NF-κB activity and favors cell proliferation, whereas the *EWSR1-FLI1* fusion inhibits NF-κB and skews the neoplastic cells towards (neural) differentiation [38]. This renders CD99 silencing a theoretically reasonable treatment strategy. Exosomes shed from CD99-silenced Ewing sarcoma cells can spread a similar pro-differentiation phenotype to CD99-non-silenced ones, and they do so by means of miR-34a, a down-regulator of Notch 1, Notch 3 and NF-κB expression in the recipient tumor cells [38].

Apoptosis ligand 2/TNF-related apoptosis-inducing ligand (Apo2L/TRAIL) is a potent pro-apoptotic and therefore possible anticancer agent, but nonetheless with only mediocre clinical efficacy so far [39]. Artificial exosome-like lipid nanoparticles carrying membrane-bound TRAIL, termed LUV-TRAIL, have been created in the image of physiologically T-cell produced TRAIL-containing exosomes [40]. Compared with soluble TRAIL, LUV-TRAIL was more efficient against sarcoma cell lines, either alone against Ewing sarcoma cells or combined with flavopiridol against fibrosarcoma and rhabdomyosarcoma cells [40]. In addition, LUV-TRAIL may suffer less from off-target toxicity in vitro [41] and in vivo [42] than soluble TRAIL.

3. Exosomes and sarcoma diagnosis, surveillance and prognosis by type of sarcoma: *Data from clinical samples*

3.1. Liposarcoma

3.1.1. Diagnosis and/or surveillance

Liposarcoma cells secrete exosomes packed with miR-25-3p and miR-92a-3p, both detectable in human plasma, which discriminated reliably (AUC: 0.86 and 0.82 respectively) 24 patients from healthy controls [43]. Both miRNAs promote liposarcoma cell proliferation, invasion, and metastasis by inducing the production of proinflammatory IL-6 from tumor-associated macrophages in a TLR7/8-dependent fashion [43].

3.2. Kaposi's sarcoma

3.2.1. Diagnosis and/or surveillance

Exosomes can serve as markers for both Kaposi sarcoma's neoplastic

cells and the concomitant Kaposi's sarcoma-associated herpesvirus (KSHV) [44]. On the basis of experimental animal- and preliminary patient-derived data, cases of Kaposi's sarcoma exhibit a different exosomal miRNA profile, which includes known oncogenic miRNAs such as miR-17-92, already implicated in the pathology of Kaposi's sarcoma [45,46], and miR-106b/25. KSHV DNA and KSHV miRNAs (miR-K2, miR-K12-4-5p, miR-K12-4-3p, miR-K12-5, miR-K12-6-5p, miR-K12-10a and miR-K12-11), but not KSHV proteins, have also been isolated from exosomes [44]. In fact, some viral miRNAs were detectable practically only in exosomes, unlike the viral DNA, which was essentially detected only in its freely circulating form or inside virions rather than inside exosomes [44].

Of note, exosomal viral miRNAs were detected also in the absence of virion formation, which makes them a likely sensitive marker of KSHV infection in the latent phase [44]. KSHV-encoded and exosome-packed miRNAs are not mere by-products of KSHV infection but also biosignalling particles able to induce the so called “reverse Warburg effect” in Kaposi's sarcoma, i.e. stromal metabolic changes in favor of the tumor [47].

3.3. Gastrointestinal stromal tumor

3.3.1. Diagnosis and/or surveillance & prognosis

The biological behavior of gastrointestinal stromal tumors (GISTs) ranges from benign to frankly malignant, which is why it is treated among sarcomas for the scope of this review. Berglund E. et al. identified the GIST secretome as a total of 764 proteins, noting that most of it is detectable in exosomes, and observed modifications in the secretome following imatinib treatment, but also depending on the cell stimulation method used [48].

A thorough proteomic study focused on exosomes identified 1060 proteins as the main GIST exosomal proteome, which includes possible diagnostic markers (e.g. KIT, CD34, ANO1/DOG1, PROM1, PRKCQ, and ENG), prognostic markers (e.g. CDKN2A, EPHA4, FHL2, DPP4, EZR, HIF1A and KCTD12) or indicators of durable and/or immediate response to imatinib (SPRY4, SURF4, ALIX, FZD8 and PDE2a) [49]. Additionally, metastatic disease was characterized by a marked increase in circulating exosome concentration as well as by a rise in exosomal SPRY4 levels [49].

3.4. Synovial sarcoma

3.4.1. Diagnosis and/or surveillance

Synovial sarcoma's molecular signature is the *SS18-SSX* gene fusion, the transcript of which has been isolated in released microvesicles [50] but not from circulating exosomes [51]. Exosomes secreted from synovial sarcoma cells contain miR-92b-3p instead, which performed fairly well as a diagnostic biomarker in a small cohort of synovial sarcoma patients against healthy controls (area under the curve/AUC: 0.77, sensitivity: 81.8%, specificity: 63.6%), as well as against patients with nine other types of soft tissue tumors. i.e. alveolar soft part sarcoma, clear cell sarcoma, dedifferentiated liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumour, myxofibrosarcoma, myxoid liposarcoma, solitary fibrous tumor and undifferentiated pleomorphic sarcoma (AUC: 0.87, sensitivity: 84.6%, specificity: 80%) [51].

3.5. Ewing sarcoma

3.5.1. Diagnosis and/or surveillance

Exosomes produced by Ewing sarcoma cell lines contain a very specific mRNA profile which involves genes implicated in G-protein-coupled signalling, neurotransmitter signalling and stemness and, most importantly, includes the transcript of the fused *EWSR1-FLI* gene [52], the driver genetic event and molecular signature of most Ewing sarcomas [53]. Other transcripts that also stand out in Ewing sarcoma's exosomal transcriptional signature are those of *NR0B1 (DAX1)*, *NKX2.2*, *STEAP1* and *LIPI* genes, largely in line with the tumor's described gene expression profile [54].

4. Discussion

Exosome-based biomarkers for sarcomas have not been tested in more than small cohorts of patients [36,43,44,48,49,51]; most data have been obtained in fact from cell lines [20–23,27,52]. Yet, promising findings have been reported.

Most interesting are the diagnostic properties of exosomes in sarcomas. In the first place, we underscore the ability to detect in exosomes highly specific, well-established diagnostic markers, i.e. the *EWSR1-FLI1* gene fusion transcript in Ewing sarcoma [52] and the ANO1/DOG1 protein in GIST [49]. One might add the case of synovial sarcoma, where the *SS18-SSX* gene fusion transcript has been isolated from released microvesicles [50], though sadly not from exosomes [51]. In the second place, we point out the discovery of new, single markers with noteworthy or potential diagnostic capacity, such as miR-92b-3p in synovial sarcoma [51], miR-92a-3p in liposarcoma [43], miR-25-3p in liposarcoma [43] and osteosarcoma [22], *EZH2* mRNA in Ewing sarcoma [36], and miR-1246 and miR-1268 in rhabdomyosarcoma [20]. In the third place, we note that - apart from single markers - exosomes also facilitate the detection of biomolecular profiles, either protein- [23,48,49], mRNA- [36,52] or miRNA-based [20,22,43,44]; the integration of multiple biomolecules in biomarker panels is a great theoretical advantage of exosomes over other liquid biopsy materials. In terms of prognosis, prediction of response to therapy and therapeutic applications, all available data are currently limited to non-human subjects, hence not yet readily applicable on a clinical level.

Comparing exosomal with “free” circulating nucleic acids it can be deduced that they do not necessarily coincide. For example, exosomes are superior in the detection of KSHV miRNAs but inferior in the detection of KSHV DNA [44]. In the case of osteosarcoma, the literature is much more abundant with various suggested miRNAs, mostly diagnostic but also prognostic and/or predictive, such as miR-497 [55], miR-326 [56], miR-21 [57–59], miR-152 and miR-24 [60], miR-421 [61], miR-214 and miR-126 [62], miR-221 [63], miR-191 [64], miR-199a-5p [59,65], miR-195-5p, miR-199a-3p, miR-320a, and miR-374a-5p [66], miR-195 [67], miR-148a [68], miR-133b and miR-206 [69], miR-9 [70], miR-143 [59], miR-29 [71], and miR-34b [72]. Serum miRNA models seem to have considerable diagnostic value in osteosarcoma [73]. In the case of rhabdomyosarcoma, the proposed diagnostic miRNA isolated from the serum (miR-206 [74]) differs from those isolated from exosomes (miR-1246 and miR-1268 [20]). For some sarcomas, such as the dedifferentiated liposarcoma and the uterine sarcoma, the literature is limited only to circulating miRNAs, such as miR-3613-3p [75], miR-152 and miR-24 respectively [60]. Conversely, to our knowledge no studies have evaluated “free” miRNAs as biomarkers in the other sarcomas reviewed here, i.e. fibrosarcoma, Kaposi's sarcoma, GIST, synovial sarcoma or Ewing sarcoma. Finally, for treatment purposes, exosomes can serve as a necessary delivery system of nucleic acids, since the latter cannot be administered systemically otherwise [15].

The above discrepancies in the literature between “free” and exosomal miRNAs can be ascribed to small sample size and/or considerable tumor heterogeneity in itself as well as across different patients. This underlines the need for large-scale studies in order to test the experimental data on a clinical level and design integrated diagnostic, prognostic and predictive models. Exosomes are particularly eligible for this purpose thanks to their stability in the circulation and their rich content comprising of a large array of biomolecules.

In conclusion, we believe that exosomes have opened up new possibilities in the management of sarcomas within the scope of personalized medicine and can spur a search for novel biomarkers.

Conflicts of interest

There is no conflict of interest.

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