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Noncoding RNA in Extracellular Vesicles Regulate Differentiation of Mesenchymal Stem Cells

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To achieve the desired outcome in tissue engineering regeneration, mesenchymal stem cells need to undergo a series of biological processes, including differentiating into the ideal target cells. The extracellular vesicle (EV) in the microenvironment contributes toward determining the fate of the cells with epigenetic regulation, particularly from noncoding RNA (ncRNA), and exerts transportation and protective effects on ncRNAs. We focused on the components and functions of ncRNA (particularly microRNA) in the EVs. The EVs modified by the ncRNA favor tissue regeneration and pose a potential challenge.

Keywords: noncoding RNA, extracellular vesicles, mesenchymal stem cell, exosome, differentiation

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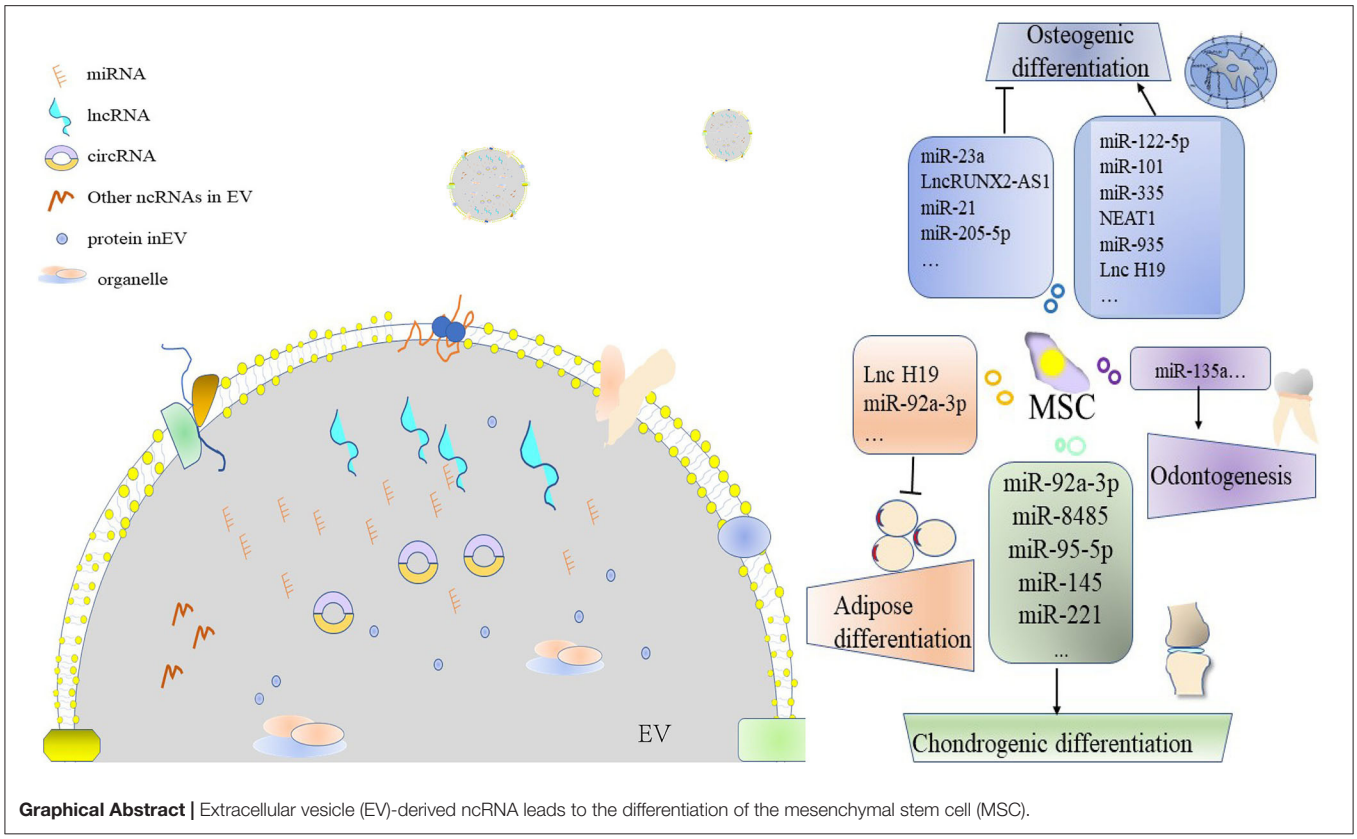
INTRODUCTION

Mesenchymal stem cell (MSC) therapy solves several problems related to the paracrine system, and it is not known for its salutary or rescue effects (1). Transplantation relies on the proliferation, self-renewal, and differentiation of the MSCs to achieve the regenerative goal, but it is limited by donator and guidelines. Cell-free therapy is also known as cell homing, which depends on the host cell under the given microenvironment to complete the task (2). The factors influencing the results of cell transplantation therapy also affect the results of cell-free therapy, including quality, reproducibility, and production potency (3). Extracellular vesicle (EV) from MSC (MSC-EV), especially highly homologous MSC, could perform tissue regeneration and immunoregulation function and help in avoiding the aforementioned problems (4). For example, bone marrow mesenchymal stem cell (BMSC) exosome rescues radiation-related bone defects, which is similar to MSC therapy (5). Exosome from dental pulp stem cells has been demonstrated to be a biomimetic tool for pulp regeneration (6). MSC-originated exosome has been shown to promote nerve regeneration in an animal model (7). The regulation of each step of regeneration by EVs is critical. Researchers have explored the bioactive content of EVs and have focused on the key aspect of noncoding RNA (ncRNA) (4). There seems to be some connection between EV and ncRNA. The parent cell targets the recipient cell *via* EV cargo, such as ncRNA, and leads to a biological process (8). Exosome from the MSC mainly inhibits immunity and attenuate injury by delivery miR-182 (9, 10). Release of exosome and microRNA (miRNA) is significant for BMSC function and bone homeostasis and can be inhibited by the simultaneous demethylation of P2rX7 (11). Shuttling cytosolic ncRNA, EVs perform epigenetic regulation as a special nano-communication system (12). The transcriptional and post-transcriptional genetic modification provides a controllable, manageable, and feasible avenue for regulating the differentiation of MSCs into lineage-specific



Graphical Abstract | Extracellular vesicle (EV)-derived ncRNA leads to the differentiation of the mesenchymal stem cell (MSC).

cells. The innate immunomodulatory activity of the MSCs is co-constructed by exosomal miRNA and the arresting domain-containing protein of the micro vesicles (13). The aforementioned crosstalk is useful for cell-free MSC therapy.

Extracellular vesicles (EVs) can be classified into three types according to their biogenesis and partial-overlap size: exosome [30–100 nm (14) or 30–130 nm], microvesicles (100–1,000 nm), and apoptotic bodies (50–4,000 nm) (4). Additionally, microvesicles are also called large size EVs (lEVs) or microparticles (MPs), and they were believed to carry cell organelles and bioactive molecules, such as ncRNA (15). According to the originating cells, EVs can be classified into tumor-derived extracellular (TEVs), outer membrane vesicles (OMVs) from bacteria, plant extracellular vesicles, and so on (16–18); furthermore, the exosomes can be distinguished into CD63, CD9, CD81, and cavelion1 subpopulations according to their immunological features of the membrane (19). The membrane of the EVs protects the RNAs from low PH (20) and helps them to resist nuclease activity (21). Because of the protective effect, low immunogenicity, and stability of the membrane, EVs serves as a potential carrier for nano-delivery treatments (22). The EVs mainly contain protein, nucleic acid, and lipid and vary based on origin and condition (12). miRNAs are prone to enrich in exosomes comparing to other EV species (23). Furthermore, the nucleotide sequence motif is the ticket for miRNA packaging into exosomes of specific types of cells (24). The plasma concentration of individual RNAs is another decisive factor (20). Blebbing from the dying cells, the apoptotic body mainly carries tightly-packed organelles, proteins, and mRNAs (25, 26). The apoptotic bodies contain miRNA, and both can activate the immune response and promote cell death (27). Along with other factors, EVs regulate the biological behavior of the target cell, such as differentiation (28). The exosome from MSC has a considerable role in oral-facial bone regeneration (29). This article summarizes the ncRNA cargo in the EV, the manner of ncRNA packaging, and the concerted effects of EV and ncRNA on the target cell.

ncRNA EXISTS IN EVS

Interest in This Field

There are several publications on EVs and ncRNA, especially exosome and miRNA, and they are increasing exponentially. For example, in 2020 alone, articles pertaining to the mentioned keywords amount to 1,390. Hence, over the past years, the topic has received immense attention, and researchers have contributed to the development of exosome-based ncRNA delivery and the biological behaviors of the recipient cells. It was first reported in 2007 that "exosomal" regulation of cell reprogramming is dependent on miRNA and mRNA (30). The genetic information of the EVs resembles that of the parent cell (12), and miRNA always serves as the biologically active material in the EV for downstream clarification (31).

The Achievement in This Field

Many types of ncRNAs, including transfer RNA (tRNA), Y RNA, ribosomal RNA (rRNA), PIWI-interacting RNA (piRNA), circular RNA (circRNA), and unannotated RNAs are contained in the exosomes (4, 32–34). It has been demonstrated that RNase I generates extracellular Y RNA and tRNA (21), and that these RNAs partially exist in the open extracellular space (35). A stress-regulated vesicle as tiRNA (tRNA) signaling approach promotes proliferation, protein translation, and differentiation (36). PIWI–piRNA complexes silence the targets during transcription *via* transporting by MSC-EVs (37, 38). The release of EVs is believed to be the clearing mechanism of circRNA from the plasma (39), while EV also protects circRNA to contain the equilibrium (40). Long noncoding RNAs (lncRNAs) from exosomes could be a biomarker for disease (41), and the lncRNA–miRNA–mRNA network has been investigated in exosomes (42). Furthermore, the network function can be described as follows: (1) function as a sponge; (2) co-expression of ncRNAs; (3) reciprocal repression; (4) role of miRNAs as negative regulators of lncRNAs (43); (5) other unconventional miRNA functions (44). Despite the continued emergence of new species, nowadays, most reports are focused on miRNA and lncRNA and great progress has been made (45).

EVs have the potential to aid in the diagnosis, research, and application because of the packaging of the cytoplasmic contents into natural lipid membranes and their shuttle through the natural barrier (46). Remarkably, miRNA selectively captured in the exosomes is partially dependent on the endosomal sorting complex required for transport (ESCRT) (47, 48), which is the classical exosome biogenesis mechanism. Furthermore, other factors are also involved in miRNA packaging. These include CD63, MHC1, CD47 (49), neutral sphingomyelinase 2 (nSMase2)-ceramide (47), miRNA associated protein of RNA-induced silencing complex (RISC) component (50), RNA binding protein(synergistical function), membrane transportation (51), and motif-binding protein of RNA binding protein (52, 53). The isolation manner also impacts the RNA cargoes *via* lipoproteins (54). The ncRNA content of the EV is also determined by the cytoplasmic level of the genes of the parent cell (12).

Naturally occurring exosomes can be transported to neighboring and remote sites *via* body fluids (55) and alter multiple genes and signaling pathways in the target cells (56). The exosomes modified by tissue engineering navigate the targets by membrane protein modification (57) or the physics method (58).

The miRNA expression undergoes striking changes based on the cell-cell communication in a specific microenvironment (59). This interaction is also named "exosome-shuttle miRNAs" (60). Remarkably, interaction also exists between the extracellular matrix and the exosome (61).

Methodology in This Field

Using the advanced methods of quantitative real-time polymerase chain reaction, microarray, and sequencing technology, genomic complexities and functions were gradually revealed by biological experiments or bioinformatic analysis. Databases, such as Exocarta, Vesiclepedia, and EVpedia, make the above information publicly accessible and develop the relevant software, thereby creating a convenient platform for upstream and downstream investigations (62). Normally, the comparison has always been set among the EVs of different origins because EVs and their originating cells always play similar roles in biological behavior. However, differential expression also exists between the originating cells and their exosomes (63, 64).

ORIGINATING CELLS CONTRIBUTE TO EV-DERIVED ncRNAS

In the early stages of life, the epigenome has been determined by both inherited and nutritional factors. Subsequently, the environmental factors become involved, that is, external stimuli (65). Cells present in the microenvironment experience various physical, chemical, and biological changes, and they can adjust themselves based on epigenetic regulation and delivery crosstalk information, such as the release of content-reprogramed EVs (66–68). Generally, MSCs from craniofacial tissues are roughly divided into BMSC, dental MSC, and adipose stem cell (ADSC) with potential for hard and soft tissue repair and regeneration. Under specific conditions (origin, inflammation, aging and apoptosis, physical stimulus, ncRNA modification, and differentiation), the cells differ in their ability to express EVs (**Table 1**).

The Expression of ncRNA in MSC-Origin EVs

Exosomes from ADSC promote neuronal survival by transporting MALAT1 (69). Microvesicles from the same parent cell promote both proliferation and migration by delivering miR-210 (70). ADSC and BMSC share highly identical small RNA profiles (mainly involving miRNA and snoRNA), and so does the exosome. However, differential expression of tRNA was observed, which could be explained by tissue origin and stemness (33). The expression of piRNA in exosomes from stem cells from apical papilla (SCAP) provides a novel insight into the functions, such as biological regulation (38). miR-1470 is one of the exosomal biomarkers of BMSCs for its high expression when exosomes from fibroblast serve as the control (71). Equipped with miR-92a-3p, miR-26a-5p, miR-23a-3p, miR-103a-3p, and miR-181a-5p, exosome from neuronal stem cell has therapeutic potential (78).

The Modification of Cells Triggers EV to Transfer ncRNAs

Macrophage polarization changes the EV function in bone repair/regeneration by adjusting enclosed miRNA (79). Inflammation modifies the loading and quality of EVs by RNA binding protein FMR1 and ESCRT pathway (80).

Aging leads to the change of exosome from BMSC, which clarifies immune-associated miRNA profiles, and toll-like receptor 4-regulating miR-21-5p is highly expressed in the pre-pubertal group (81). Similarly, the upregulation of miR-128-3p

TABLE 1 | A summary of several common ncRNA derived from extracellular vesicles (EVs) of mesenchymal stem cells (MSCs).

Noncoding RNA- target gene	Target cell	Parent cell and EV type	Biological behavior
MALAT1- PKCδII (69)	HT22 neuronal cells	ADSC and exosome	Survival and proliferation
miR-210-RUNX3 (70)	human umbilical vein endothelial cells	ADSC and microvesicle	Proliferation, migration and invasion
miR-1470-c-Jun (71)	CD4 + CD25 + FOXP3 + Tregs	BMSC and exosome	Differentiation
miR-128-3p-Smad5 (72)	MSC	aged MSC and exosome	Inhibition of osteogenic differentiation
miR-31a-5p-SATB2 (73)	BMSC	BMSC from aged rats and exosome	Osteoclastogenesis
miR-126-SPRED1 (74)	human umbilical vein endothelial cell	hypoxic human umbilical cord MSC and exosome	Angiogenesis, proliferation and migration
miR-181c-TLR4 (75)	macrophages	human umbilical cord MSC and exosome	Inflammation reverse
H19-miR-106-Angpt1 (76)	/*	BMSC and exosome	Osteogenesis and angiogenesis
miR-122-5p, miR-25-3p, and miR-142-5p Δ (77)	rat BMSCs	Osteogenic differentiated human periodontal ligament stem cell and exosomes	Osteogenic differentiation

**This conclusion is derived from experiment in vivo.*

Δ *This article does not involve downstream functional verification.*

in the exosome of the BMSC of an aged mouse inhibits fracture healing (72). miR-31a-5p from BMSC exosome of aged rats promotes osteoclastic and attenuates osteoblastic differentiation, which is similar behaviors when compared with its origin (73). Staurosporine-treatment results in ribosomal RNA cleavage and degradation (82).

Hypoxia preconditioning changes the content of miR-126 in the exosomes from MSCs and makes it fit for bone fracture healing (74). Hypoxia also induces angiogenic miR-135b to increase expression in exosomes (83). Mechanical strain upregulates miR-181b-5p in the exosomes of osteocytes (84).

miRNA-modified originating cell leads to the same miRNA increase in the exosome. In other words, transfection of miRNA can promote the secretion of itself in the supernatant (4, 85). For example, miR-181-5p modified adipose stem cell delivers therapeutic EV to the damaged site and contributes to recovery *via* activating autography (86). miR-181c-overexpressed MSC exosome significantly reduces the burn origin inflammation (75). Exogenous mimic or inhibitor has been reported to regulate the downstream cell with more efficiency and less toxicity compared with the conventional manner (87). Microvesicles from miR-34a overexpressing BMSC carry three-fold higher miR-34a than the control (88). Transfection of miR-20a makes BMSC-EV favorable for alveolar bone-implant osteointegration *via* pro-osteogenic effects (89). Similarly, osteogenic differentiation-related to miR-375 can be capsulated by adipose stem cell exosome and the exosome can induce BMSC osteogenic commit (90).

During osteogenesis, BMSC releases lncH19-containing exosomes which have been validated by observing the bone microstructure of immunocompromised nude mice (76). Osteogenic induction modifies the EV cargoes of PDLSC with miR-122-5p as the top one by miRNA differential expression analysis (77). Moreover, different cell types possess distinct RNA profiles (91), and the miRNA in adipose-derived exosomes is related to insulin-associated metabolism (92).

EV-DERIVED ncRNA INDUCES DIFFERENTIATION

The biogenesis of EVs is implicated in a series of biological processes, including the differentiation of MSCs. Exchange of EV ncRNA cargo is also important in achieving cell population homeostasis between the progenitor cell and the differentiated cell (93). RNase completely abolishes the biological effect of exosome-like microvesicles, which indicates the participation of RNA-like components (94, 95). EV reprograms MSCs and makes them produce more specific EVs to disseminate miRNA and mRNA (96).

EV-Derived ncRNA Induces Osteogenic Differentiation

Exosomes carrying miR-122-5p negatively regulate SPRY2 to initiate osteoblastic phenotypes (97). Radiation-induced gingival fibroblasts highly express miR-23a in their exosomes, thereby resulting in the osteogenic differentiation of BMSC (98). The lncRNA RUNX2-AS inhibits the key osteogenic regulator—, RNUX2, by the transportation of exosomes (99). miR-21/Smad7 axis detected by the exosome of BMSC is the mechanism of negative osteogenesis in osteoporosis patients (100). After 21 days of osteogenic inducement, miR-101 is upregulated in BMSC-derived exosomes, and the target demonstrates osteogenic potential upon functional verification (101). miR-335/VapB/Wnt/β-catenin axis promotes bone fracture recovery and osteoblast differentiation, which is attributed to BMSC-derived EVs (102). Osteogenic and odontogenic lineage progression includes the epigenic involvement of RUNX2 and BMP2 (103, 104). Furthermore, exosomal miR-135a enhances the output of the dentin matrix *via* Wnt/β-catenin signaling pathway and contributes to tooth development (105). NEAT1-containing exosomes induce BMSC osteogenic commitment by sponging miR-205-5p (106). MiR-223 decreased exosomes promote differentiation into osteoblasts (107). Exosomes from

BMSC promote osteoblast proliferation and differentiation by releasing STAT1-targeting miR-935 (108).

EV-Derived ncRNA Induces Chondrogenic Differentiation

Exosomal miR-92a-3p regulates chondrogenic development by directly targeting Wnt5A and therefore holds therapeutic potential in osteoarthritis (109). Chondrogenic differentiation also makes the BMSC exosomes highly express 35 kinds of miRNA, including miR-92a (110). Chondrocytes induce BMSC chondrogenic differentiation *via* the delivery of miR-8485-containing exosomes in a co-culture system (111). miR-95-5p is overexpressed in the chondrocytes, and the chondrocytes in turn produce chondrogenic exosomes, which can inhibit HDAC2/8 (112). Adipose stem cells deliver exosomal miR-145 and miR-221 to regenerate the cartilage and ameliorate osteoarthritis (113).

EV-Derived ncRNA Induces Angiogenic Differentiation

Vascularization is considered the key factor for successful transplantation and regeneration as vascular supply necessary nutrition and oxygen. Stem cells from deciduous teeth (SHED) aggregates secrete miR-26-enriched exosomes to forge a suitable microenvironment for pulp regeneration (114). Serum exosomal miR-1956 stimulates the angiogenic differentiation of adipose stem cells by activating Notch-1 (115).

EV-Derived ncRNA Induces Neurogenic Differentiation

miR-17-92 cluster-enriched MSC-exosomes augment neural plasticity and functional recovery by regulating the cluster target gene (116). Transferring exosomal miR-133b and miR-124-3p regulates nerve outgrowth and neurological disease recovery and reduces neuroinflammation (117, 118). miR-126-loaded MSC exosomes may be a candidate for the treatment of neurological injury, with excellent angiogenic and neurogenic potentials (119). MSC exosomal miR-199a-3p/145-5p plays a critical role in neuronal differentiation (120).

EV-Derived ncRNA Induces Adipogenic Differentiation

Exosomal miR-92a-3p regulates C/EBPα at the post-transcriptional level to block adipogenic differentiation of adipose stem cells (121). Obesity and high-fat treatment break the bone–fat equilibrium and downregulate the expression of lnc H19 in the circulation and output of BMSC-origin exosomes (122).

CHALLENGES AND PROSPECTS

Although organelles, cytokines, and lipids enrich EV constituents (123), this review implicates ncRNA. To facilitate clinical translation, high purity, low cost, and largescale exosome isolation techniques need to be developed (124). 3D culture and isolation by tangential flow filtration can potentially pave the road from bench to bed (125). A specific aptamer for exosomal application is also necessary since the exosomes significantly enhance the osteoblastic differentiation of BMSC *in vitro* but not *in vivo* (126).

Largescale studies on RNA according to the miRNA nomenclature guidelines are also inadequate; so are the studies on clusters and other EV-derived ncRNAs (excluding lncRNA and miRNA). Moreover, the autocrine system is an issue worth exploring (127).

It is hoped that EVs would be a better drug vehicle than lipids since they can pass natural biological barriers (128, 129) or exert functions with their anatomical apposition (130). They are safe for use in the field of oncology and can be modified using multiple methods (131). Moreover, "EV encapsulated RNA drugs" combined with engineering modification is a powerful cell-free gene therapy tool that holds considerable promise for regenerative therapy in the future.

AUTHOR CONTRIBUTIONS

CY contributed to the design and conception, manuscript writing, and final approval of the manuscript. JY contributed to the design and conception, manuscript revising, financial support, and final approval of the manuscript. Both authors have read and approved the final version of the manuscript.

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