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Regenerative effects of mesenchymal stem cell-derived exosomes

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssalen på våning 5, avdelningen för biomaterialvetenskap, Arvid Wallgrens backe 20, fredagen, den 1 mars, 2019, klockan 13.00 av

Xiaoqin Wang

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

I. Wang X, Omar O, Vazirisani F, Thomsen P, Ekström K. Mesenchymal stem cell-derived exosomes have altered microRNA profiles and induce osteogenic differentiation depending on the stage of differentiation. *PLoS One.* 2018; 13(2): e0193059.

II. Wang X, Philip J, Vazirisani F, Tsirigoti C, Thomsen P, Ekström K. The impact of *in vitro* aging on the release of extracellular vesicles from human mesenchymal stem cells. *In manuscript.*

III. Wang X, Shah FA, Vazirisani F, Johansson A, Palmquist A, Omar O, Ekström K, Thomsen P. Exosomes influence the behavior of human mesenchymal stem cells on titanium surfaces. *Submitted for publication*.

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Regenerative effects of mesenchymal stem cell-derived exosomes

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Abstract

Mesenchymal stem cells (MSCs) play pivotal roles for bone regeneration by virtue of their osteogenic differentiation ability and immunomodulatory capacity. Recently, secretion of exosomes/extracellular vesicles (EVs) has been suggested as a new mechanism of MSC-based therapy. MSC-derived EVs/exosomes have shown promising effects in tissue regeneration and immunomodulation, which are attributed to their regulatory effects in various processes. The overall objective of this thesis was to explore the cell-to-cell communication and cell-to-material surface interaction mediated by MSC-derived EVs/exosomes. The emphasis was placed on their functions in the regeneration capacity of MSCs and the determination of the microRNA and protein contents of these EVs/exosomes in order to obtain an insight into the underlying mechanisms of the EV-/exosome-mediated biological effects.

The results demonstrated that exosomes secreted from MSCs in the mid and late stage of osteogenic differentiation induced osteogenic lineage commitment, but only exosomes from the late differentiation induced the mineralisation of the extracellular matrix. MSC-derived exosomes were internalised by a subpopulation of homotypic cells. The differentially expressed microRNAs were osteogenesis related and predicted to enrich pathways involved in the regulation of osteogenic differentiation and general mechanisms by which exosomes exert their functions. *In vitro* ageing increased the secretion of EVs and in some contexts altered the protein profiles of EVs. The top abundant proteins in high passage (HP, “aged”) and low passage (LP, “young”) EVs shared similar but not identical functional features with an overlap of the enriched pathways related to endocytosis and regulation of cell proliferation and survival. The differentially expressed proteins in HP EVs were predicted to enrich GO biological process related to transport and secretion. Both HP and LP EVs promoted MSC proliferation in autocrine and paracrine manners and in a dose-dependent fashion. In contrast to MSC-derived exosomes in suspension, exosomes which were immobilised on titanium (Ti) surfaces accelerated and increased MSC adhesion, influenced the early morphology and promoted the growth of MSCs on titanium. Proteomic analysis of the exosomal protein revealed identified proteins with predicted GO molecular function related to adhesion, structure and morphology, and growth factor and growth factor receptor activity.

In conclusion, MSC-derived EVs/exosomes possess regenerative effects, in terms of the stimulation of the proliferation and osteogenic differentiation of MSCs, and influence the behaviour of MSCs on titanium surfaces. The expression of exosomal cargoes is altered during osteogenic differentiation and *in vitro* ageing and their predicted functions partially correspond to the observed effects. It is suggested that the MSC-derived EV-/exosome-mediated effects on the regeneration capacity of MSCs are at least partially attributed to the transfer of functional exosomal cargoes.

Keywords: aging, cell adhesion, cell-material interaction, exosomes, extracellular vesicles, mesenchymal stem cells, osteogenic differentiation, proliferation, regeneration, titanium

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