Molecular and cellular mechanisms of pro-regenerative activity of stem cell- derived extracellular vesicles (EVs) in ischemic myocardial injuries: Role of microRNAs

Extracellular vesicles (EVs) represent vesicular submicron structures including a fragment of biological membrane enclosing a part of cytoplasm of the producing/ donor cell, which may be actively produced and released by several living cells, including human stem cells (SCs). EVs have been recently extensively studied due to their active role in cell-to-cell communication, which is mediated by several bioactive molecules transferred the vesicles between cells and results in functional changes in target cells.

Interestingly, growing recent evidence indicated that EVs released from various types of SCs may transfer bioactive molecules for these premature cells to other somatic, terminally differentiated cells and as such mediate tissue repair in injured tissues and organs, including in infarcted heart. Since distinct SC populations release vesicles with distinct molecular cargo – containing different bioactive molecules, several recent studies have been focused on biological and por-regenerative activity of EVs derived form several SC populations including induced pluripotent SCs (iPSCs) and mesenchymal SCs (MSCs) – the adult SCs originated from various adult tissues including bone marrow, fat and also post-delivery umbilical cord.

In our recent studies, we have established that EVs released form both iPSCs (iPSC-EVs) and MSCs (MSC-EVs) carry several molecules reflecting molecular content of their parental/ donor cells including not only proteins, but also mRNA molecues and small regulatory microRNAs (miRNA), which play vast role in regulating expression of several important genes. Interestingly, we have found that such molecular cargo may be transferred *via* SC- derived EVs to cardiac cells and significantly impact on their functional performance *in vitro* and *in vivo* after transplantation.

Altough, both EV fractions may enhance pro-regenerative capacity of cardiac tissue, they carry several unique and distinct molecules, including large clasters of miRNA, which may differently regulate functions of various cardiac cell types present in human heart, which has not been well studied.

Thus, to better understand the mechanisms underlying pro-regenerative properties of selected EV fractions, we would investigate a role of selected miRNA molecules carried by EVs, in various types of cardiac cells, both *in vitro* and *in vivo*. We will utilized molecular strategy to silence expression of selected miRNAs to evaluate biological properties of such modified EVs on molecular and cellular functions of cardiac cells.

The result of the project will not only provide new knowledge and better understanding of mechanism underlying pro-regenerative capacity of various types of SC- derived EVs in heart tissue, and may also potentially provide some new perspectives for improving human heart tissue repair after ischemic heart injury in patients.