HUMAN-CELL MICROPARTICLES FOR CELL-THERAPY AND CARGO DELIVERY TO STEM CELLS

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Cell-derived microparticles (MPs) are vesicles budding from cellular plasma membrane under stress or activation, range from 0.1 to 1 micron in size. MPs, which are distinct from the smaller exosomes, are found to be important in cell-cell communication through transferring cargo such as RNAs, proteins, and lipids from parent cells to target cells. We work with megakaryocytic MPs (MkMPs), which are the most abundant MPs in circulating blood. MkMPs are derived from megakaryocytes (Mks) which are derived from hematopoietic stem and progenitor cells (HSPCs). We have previously shown that MkMPs target HSPCs to program them into generating megakaryocytes (Mks) leading to platelet generation without addition of thrombopoietin. The recognition is specific for HSPCs and the outcomes specific for Mk and platelet generation. We have also shown that uptake of MkMPs by HSPCs is though both some endocytotic process had membrane fusion. We carried out studies to enhance our understanding of the process of target recognition and specificity with the ultimate goal of using MkMPs for cell therapy and cargo-delivery applications. Using various inhibitors, we show that macropinocytosis and lipid rafts play an important role in the uptake of MkMPs by HSPCs. We also describe that MkMPs target and enter HSPCs in the HSPC uropod (“tail”), which helped us identify the specific surface antigens, mostly on HSPCs, that are responsible of mediating the recognition and uptake process of MkMPs. To pursue therapeutic applications, we present data involving transfusion of MkMPs in a murine model with and without induced thrombocytopenia. We also discuss methods for loading MkMPs with exogenous cargo for delivery to HSPCs, and the development of tools to visualize the cargo delivery.