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POSTER 20: Functional , proteomic and metabolic profile of Mesenchymal Stromal Cells in ischemia-like environment

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Mesenchymal Stromal Cells (MStroCs) comprise multipotent stem cells capable to regenerate the injured tissue upon ischemic insult. Yet, high post-transplantation MStroCs mortality is evidenced upon their engraftment. Therefore, exploring the strategies aiming at *improving* cell transplant viability is the challenge for cell therapy. To this end, functional, bioenergetic omics and metabolic analyses of bone marrow MStroCs issued in anoxia (O2 deprivation) and ischemia-like condition (anoxia/aglycemia, O2 and glucose deprivation, AA) were carried out. MSC cultured at optimal physiogical 3% O2 are used as control. In our work, functional tests reveal that MStroCs exhibit complete proliferative and differentiation properties in anoxia. Also, functional single cell and gene expression analyses revealed that MStroCs are not only maintained in AA condition but are those in which stem cells with the highest proliferative and differentiation capacity are the most enriched. ATP and lactate production analysis reveal that the energy needed in anoxic condition are met mainly by glycolysis and lipid metabolism. In contrast, energetic homeostasis in AA is partially provided by anaerobic mitochondrial activity engaging mitochondrial complexes (I-III) (assayed by mitochondrial marker sTOMM20, TMRM, as well as Seahorse and Oroboros measurements). Metabolic analyses evidenced a significant succinate accumulation in this condition. This is partially due to a reversal of

succinate dehydrogenase, which in turn is driven by fumarate overflow from purine nucleotide breakdown and a malate aspartate shuttle activity. However, the major pathways contributing to the succinate accumulation comprise the stimulation of glycogen-driven glucose/pyruvate, as well as ketone body, fatty amino acid, and propanoate metabolism that provide succinyl-CoA-converted succinate in substrate level energy-generated reaction. Furthermore, MStroCs ischemia survival is related to sulfide metabolism (detected as an increased sulfide quinone oxidoreductase (SQR) and thiosulfate sulfurtransferase activity as well H2S consumption. Moreover SQR-mediated oxidation of H2S drives reverse electron transport at mitochondrial complex I, using as glutathione as electron acceptor. Our findings evidence great metabolic MStroCs flexibility. Harnessing this ex vivo conditioning in ischemia mimicking condition could be a strategy to enhance the MStroCs survival implanted in hypoxic/ischemic tissue.