**A proteomic understanding of the immunomodulatory mechanisms of human islet-derived progenitor cells**

Background and Aim: Type 1 Diabetes (T1D) is an autoimmune disorder that affects millions of people world-wide. In T1D, insulin-producing pancreatic beta cells are killed by the immune system, resulting in insufficient insulin production. Targeting immune cells is therefore a promising approach for treating T1D. We observed that human islet-derived progenitor cells (hIPCs) are mesenchymal in nature and have the capacity to significantly inhibit *in vitro* proliferation of different immune cell subsets, a process known as immunomodulation. The ability of hIPCs to affect immune cells through direct cell-cell contact or via indirect mechanisms offers the possibility to uncover molecules that can be therapeutically exploited for novel therapies in T1D. We therefore aimed to understand the proteins involved in immunomodulatory processes mediated by hIPCs.

Methods: We set up co-culture of hIPCs with activated peripheral blood mononuclear cells (PBMCs) and collected the supernatant. We then used unbiased untargeted bottom-up liquid chromatography-tandem mass spectrometry (LC-MS) proteomic analysis to identify differentially expressed proteins.

Results: A total of 1125 proteins were identified across 3 experimental groups. Interleukin-6 (IL-6), interleukin-8 (also called CXCL8), plasminogen activator inhibitor 1 (PAI1) and metalloproteinase inhibitor 1 (TIMP1) were differentially expressed in co-culture vs stimulated PBMCs conditions. Notably, IL-6 and CXCL8 were also differentially expressed between hIPCs and co-culture conditions, along with C-C motif chemokine 2 (CCL2) and Beta-2 microglobulin (B2M).

Discussion and conclusion: IL-6 and CXCL8 may be involved in priming hIPCs, which is essential for the induction of this immunomodulatory phenotype and PAI1 and TIMP1 may be involved in the immunosuppressive mechanisms of hIPCs. Emerging evidence suggests that immune-based therapies are effective in delaying the onset and slowing down the progression of T1D. Our results have identified proteins involved in hIPCs priming and immune cell regulation, which can lead to immune-targeting cell-free therapeutics for individuals living with T1D.