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Crosstalk of human mesenchymal stromal cells with the cellular components of the immune system

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Novum Lecture Hall (4th floor, Hälsovägen 7, Karolinska University Hospital Huddinge).

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ABSTRACT

Using the potential of immune regulatory cell populations for cellular therapy constitutes an attractive tool to obliterate imbalances of immune responses in inflammatory disorders. In this context, adoptive transfer of mesenchymal stromal cells (MSCs) represents a relatively novel approach and its impact on the immune system has not been completely clarified. In this thesis we aimed to study the effects of MSCs on key immune cell types, which led us amongst others to investigate regulatory T-cells (T_{Regs}), and myeloid cells.

We show that MSCs utilize the anti-oxidative, immune regulatory enzyme hemeoxygenase-1 (HO-1) for suppressing T-cell activation directly and for inducing T_{Regs} (=indirect T-cell suppression). An inflammatory milieu generated by alloreactive T-cells led to the so-called 'licensing' of the MSCs boosting their regulatory capacity. Interestingly, HO-1 expression was substantially diminished during this process and its functions were taken over by other (up-regulated) molecules such as cyclooxygenase-2 thereby highlighting (functional) MSC plasticity.

Most MSC-based trials lack a systemic immune monitoring, which is key for interpreting the *in vivo* effects of MSCs. Performing a comprehensive flow cytometry-based immune screening in patients with acute graft-versus-host disease (aGVHD), treated with either third-party MSC or placebo infusions (in a double-blinded fashion), we were - most importantly - able to further corroborate the notion that MSCs function *in vivo* partly by promoting T_{Reg}-subsets. Thereby, our data underscores the need for accompanying extensive immune analyses to better comprehend such "bench-to-bedside" approaches. Accordingly, we carried out thorough, laboratory investigations when we were the first to apply MSCs in a patient with treatment-refractory hemophagocytic lymphohistocytosis. Upon MSC infusion we could observe an increase of the immune modulating cytokine interleukin (IL)-10 in the serum and a preferential appearance of regulatory type 2 macrophages in the patients' bone marrow. Altogether, this data confirmed previous findings from *in vitro* and animal model studies regarding the MSCs' impact on myeloid cell populations. Driven by these observations we sought out to assess whether MSCs induce so-called myeloid derived suppressor cells (MDSCs) in aGVHD patients. Although we did not find an MSC-associated effect, we were the first to identify monocytic $CD14^{+}HLA\text{-}DR^{low/neg}$ MDSCs accumulating after allogeneic hematopoietic transplantation. We characterized their suppressive function (*via* indoleamine-2,3-dioxygenase) and established a significant association with inflammatory cytokines and aGVHD. In fact, our data indicates that MDSCs are part of an immune regulating feedback mechanism that is activated during hyper-inflammations (such as in aGVHD).

Overall, our results indicate that immune regulatory populations play a decisive role in various inflammatory diseases and MSCs could boost their responses. Furthermore our work suggests that combining basic and translational research is pre-requisite for understanding the MSCs' multifaceted interactions and for optimizing their clinical use.

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