

COMPLEMENT REGULATES THE SUPPRESSIVE ACTIVITY OF MESENCHYMAL STEM CELLS ON DENDRITIC CELL DEVELOPMENT VIA IL-6

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Introduction: Complement is a pivotal part of the innate immunity. To impact any cells, complement needs to be activated and C3 is the central component of complement activation. Although it is known that mesenchymal stem cells (MSCs) suppress immune responses via many mechanisms including inhibiting dendritic cell (DC) generation from their precursors, whether complement plays any role in this process remained completely unknown.

Methods: WT, C3^{-/-} and C5aR^{-/-}C3aR^{-/-} MSCs were isolated from femur bone marrows (BM) of 6 week old female WT, C3^{-/-} and C5aR^{-/-}C3aR^{-/-} mice (all on C57BL/6 background) using MesenCult Media (Stem cell Inc, Canada) according to the manufacturer's protocol. DCs were propagated from WT mouse BM in the absence or presence of respective MSCs at different ratios together with 4 ng/ml GM-CSF and 1000U/ml IL-4. The development and function of DCs were examined by CD11c staining and IFN γ /IL-17 ELISPOT assays. IL-6 levels in the coculture supernatants were measured by ELISA. To determine the role of IL-6 in the immunosuppressive activity of MSCs, rIL-6 was added into the MSCs/BM cell co-cultures, and the phenotype/function of the propagated DCs were examined again using methods described above.

Results: Consistent with previous reports, WT MSCs significantly inhibit GM-CSF and IL-4 induced DC generation from BM cells. Compared to BM cells co-cultured with WT MSCs, BM cells co-cultured with C3^{-/-} MSCs result in increased numbers of CD11c⁺ DCs and consequently, elevated Th1/Th17 T cell responses as assessed by flow cytometry and respective IFN γ /IL-17 ELISPOT assays. IL-6 levels in the C3^{-/-} MSCs cocultures are 3 fold lower than that in the WT MSCs cocultures and supplementing rIL-6 partially restores C3^{-/-} MSCs' immunosuppressive activities. C5aR^{-/-}C3aR^{-/-} MSCs exhibit similar impaired immunosuppressive activity as C3^{-/-} MSCs together with decreased levels of IL-6.

Conclusion: complement locally produced by MSCs is required for their efficient suppression of DC development and function, and this effect could be mediated by autocrine C5aR/C3aR signaling regulated IL-6 production in MSCs.