The development of an immune suppressive microenvironment plays a primary role in the growth of tumors and represents a major obstacle in the success of tumor immunotherapy. The metabolism of the non-essential amino acid L-Arginine (L-Arg) through the enzyme arginase I in myeloid derived suppressor cells (MDSCs) is a fundamental mechanism and prime example of the suppressive immune responses in tumor-bearing hosts. Accordingly, the depletion of L-Arg through a pegylated form of human recombinant arginase I (PEG-Arg I) impaired T cell function and delayed the appearance of graft vs. host disease in mice undergoing mismatched bone marrow transplantation (1). Additional results indicated that PEG-Arg I therapies induced the accumulation of MDSCs, suggesting that PEG-Arg I blocked T cell responses mainly through MDSC promotion (2). However, the specific mechanism by which L-Arg deprivation by PEG-Arg I impairs T cell function through an arrest of dendritic cell differentiation remains entirely unknown. In this study, we aimed to determine the effect of PEG-Arg I in the accumulation of their precursors, MDSC. Therefore, PEG-Arg I-based therapies represent a potential therapy for conditions such as self-reactive immune pathologies or T cell immunotherapy. The metabolism of the non-essential amino acid L-Arginine (L-Arg) through the accumulation of MDSCs increases in vivo through the induction of MDSCs. These results show that the treatment with PEG-Arg I impairs T cell proliferation in vivo through the accumulation of MDSCs. Additional findings also indicated that PEG-Arg I blocked the development of dendritic cells in vitro and significantly inhibited their ability to activate T cells. These results, associated with an increased accumulation of MDSCs, suggest that PEG-Arg I blocks dendritic cell differentiation, leading instead to the maturation of dendritic cells, the ultimate antigen-presenting cells. We hypothesize that L-Arg deprivation by PEG-Arg I blocks the ability of dendritic cells to efficiently activate T cells.

Hypothesis

PEG-Arg I blocks the maturation of dendritic cells, leading to the accumulation of their precursors MDSCs.

Normal Conditions

Bone Marrow → MDSC → Dendritic Cell

PEG-Arg I Induced Conditions

PEG-Arg I

Bone Marrow → MDSC → Dendritic Cell

Conclusions

• PEG-Arg I inhibits T cell proliferation in vivo through the induction of MDSCs.
• PEG-Arg I impairs maturation of dendritic cells in vitro; resulting in greater number of MDSCs.
• PEG-Arg I blocks the ability of dendritic cells to efficiently activate T cells.

Future experiments will be done to determine the role of CD11b+ GR1+ in the decreased function of dendritic cells developed in the presence of peg-Arg I and to characterize the pathways by which peg-Arg I prevents myeloid cell maturation. Another set of experiments will identify the effect of L-Arg deprivation in the maturation of dendritic cells in vivo.

References


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