SLAM-FAMILY RECEPTORS IN THE REGULATION OF CD40L-INDUCED DENDRITIC CELL RESPONSES

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Background and objectives:
Dendritic cells (DCs) regulate both adaptive and innate immune responses. Activation of immature DCs (IDCs) by Toll-like receptors (TLR) and/or interaction with CD40L cause the maturation of DCs. However, the diversity of DC-responses requires concomitant signaling of various co-receptor molecules including several members of the SLAM receptor (SLAMF) family. Similar to monocyte-derived DCs (mDCs), plasmacytoid dendritic cells (pDCs) are chief regulators of both innate and adaptive responses and offer high degree of flexibility in directing differentiation of effector T-cells depending on the maturation signals and co-receptor signaling. pDCs are capable of promoting the differentiation of Th1, Th2 Th17 or Treg cells based on environmental clues. Despite the abundance and the clearly strong immune modulatory function of SLAMF-receptors, their role in the regulation of DC functions is poorly understood. We have previously shown that SLAMF1 is inhibitory to CD40-induced cytokine responses in mDCs suggesting the existence of a feedback loop controlling inflammatory responses. Here we seek to identify the impact of SLAMF5 on mDC and pDC functions induced by CD40 signaling.

Methods and results:
We used human mDCs or the pDC-line Gen2.2 cell line that were stimulated by soluble or cell surface expressed CD40L alone or in combination with cell surface-expressed SLAMF1 or SLAMF5. Under these conditions both mDCs and Gen2.2 cells become potent antigen presenting cells expressing high levels of co-receptors (CD80, CD83, OX40L, ICOSL) and produce pro-inflammatory cytokines (IL-6, IL-8, IL12 and TNFα). In addition to CD40L Gen2.2 cells also received activation signals via TLR7 or TLR9. Gen2.2 cells activated by CD40L and Imiquimod or CpG-B upregulated CD83 and OX40L expression which was augmented by the presence of SLAMF5 while production of inflammatory cytokines was decreased. These effects were SLAMF5-dependent as they were reversed by silencing of SLAMF5 expression by specific siRNA. Interestingly, we also found that SLAMF5/SLAMF5 homoassociation increased the capacity of CD40L and TLR7L-activated Gen2.2 cells to support T-cell proliferation. The effect of SLAMF5 signaling on instructive signals driving differentiation of various T-cell subsets is underway. To date we have shown that phosphorylation of the p38 map-kinase is increased in the presence of SLAMF5 signaling.

Conclusions:
We propose that similar to SLAMF1, SLAMF5 is an inhibitory receptor in dendritic cells controlling exuberant inflammatory responses induced by both plasmacytoid and myeloid DCs and thus, may have significant influence on the regulation of tolerogenic versus immunogenic character of DCs.

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