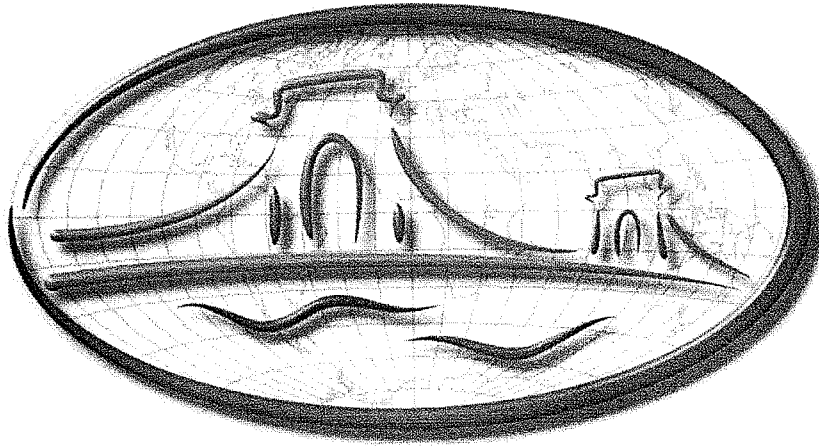




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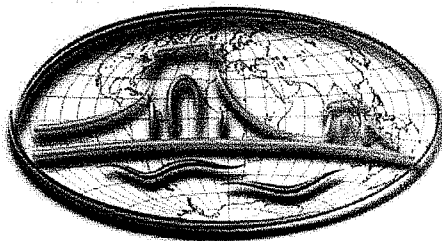
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Cell surface receptor SLAMF5 enhances DC-autophagy via IRF8

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Introduction: Recent studies have identified autophagy as both an evolutionary conserved, critical process for maintenance of cellular homeostasis and an integral part of the immune response. By controlling dendritic cell (DC) functions it facilitates immune-surveillance as well as guards against excessive inflammation. In light of the recently established link between autophagy and SLAMF receptors, we decided to examine the role of SLAMF5 in DC autophagy and in the cytokine production of DCs responding to inflammatory signals.

Methods: We performed RNA-interference targeting SLAMF5, IRF8 or SLAMF5 in combination with TRIM21 on freshly isolated monocytes, then differentiated them into DCs in the presence of GM-CSF and IL-4. To mimic infection with Gram-negative bacteria, cells were treated with LPS and IFN γ and then changes in DC functions were monitored in the absence of the above proteins.

Results: In DCs lacking SLAMF5 we found decreased autophagic flux both in the presence and absence of inflammatory stimuli. LPS/IFN γ treatment of SLAMF5-deficient DCs significantly increased production of IL-1 β and IL-23, while IL-12 secretion was diminished. Strikingly, we detected greatly reduced protein levels of the autophagy regulator IRF8, which could be reversed in the presence of the proteasome inhibitor MG132. Furthermore, silencing of TRIM21, an E3 ubiquitin ligase, completely restored the level of IRF8 in SLAMF5 knock down cells. In addition, DCs made IRF8-deficient by RNA interference showed similar characteristics to those lacking SLAMF5.

Discussion and Conclusion: Taken together, data presented in this work indicate that SLAMF5 enhances autophagy and controls pro-inflammatory cytokine production of human DCs, presumably by inhibiting TRIM21 dependent proteasomal degradation of the autophagy master regulator transcription factor IRF8. As autophagy plays a key role in the pathogenesis of several human diseases including infections, cancer, autoimmune and neurodegenerative disorders, identification of cell surface receptors regulating autophagy may improve the clinical management of these conditions.

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