THE EXRESSION PROFILE OF TAM AND NLR RECEPTORS UPON IMMUNE CHALLENGE AND CHRONIC INFLAMMATION

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Pattern Recognition Receptors (PRRs), which recognize distinct pathogen-associated molecular patterns have a pivotal role in the efficient defence against invading microorganisms. For example, activation of different Toll-like receptors induces the secretion of proinflammatory mediators resulting in local inflammatory properties. However, innate immunity must be properly controlled, as its continuous activation leads to the development of chronic inflammation.

The TAM family (TYRO3/AXL/MER) of receptor tyrosine kinases and their ligands GAS6 and protein S regulate, among others, erythropoesis, development of oligodendrocytes, phagocytosis of apoptotic cellsand immune system.Apart functioning as intracellular PRRs, members of theNLR (NOD-like receptor) receptor family also play important roles in the formation of inflammasomes (eg. NLRP3, NLRC4), regulation of the expression of major histocompatibility complexes (eg. CIITA, NLRC5) and negative regulation of immune response (eg. NLRC3, NLRC5, NLRP6). Perturbation of signallingthrough either TAM or NLR receptors leads tocontinuous and increased expression of proinflammatory effector molecules,a hallmark of autoimmune diseases, such as psoriasis.Thus, the aim of this study was to determine how the expression of TAM and NLR receptors and proinflammatory molecules correlates upon innate immune response. To this end, epithelial cells (eg. keratinocytes and vaginal epithelial cells) and monocytes were treated with distinct microbial agents (such as PGN, poly I:C and LPS) and the gene-, and protein expression profile of TAM and NLR receptors and proinflammatory cytokines/chemokines were investigated by QPCR, Western-blot and immunofluorescence labelling. As expected, microbial agents induced the expression of proinflammatory molecules, in contrast, the expression of TAM and NLR receptors is mostly down-regulated.

Since the continuous expression of proinflammatory molecules characterizes pathologic conditions such as Inflammatory Dowel Disease (IBD) and psoriasis, we next sought to determine the expression profile of TAM and NLR receptors *in vivo*in 2,4,6-trinitrobenzenesulfonic acid-induced rat model of IBD, imiquimod-induced mouse model of psoriasis and in psoriatic patients. Our results show that in parallel with the markedly upregulated expression of proinflammatory effector molecules, the expression of negative regulatory molecules is also altered, predominantly decreased.

Taken together, our results strongly suggest that the down-regulation of TAM and NLR receptor expression modifies the expression profile of proinflammatory molecules thereby inducing chronic inflammation.