Post-transcriptional control of cytokine production by intestinal macrophages

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Distinct populations of mononuclear phagocytes have been identified that have unique functional roles in maintaining immunological homeostasis in the intestine. We and others have previously demonstrated that two populations of macrophages in the colon that express MHCII, F4/80, and high or low levels of CD11c have unique gene expression profiles and produce high levels of IL-10 and IL-1R-antagonist, but low levels of TNF IL-1, IL-12, and IL-23 either constitutively or when activated with LPS or other TLR ligands *in vitro* indicating their anti-inflammatory functions. Furthermore, the activation of the NLRC4, but not the NLRP3 inflammasome was reported in intestinal CD11b+ cells, that includes DCs and macrophages indicating a mechanisms for differential recognition of pathogenic and commensal microbes through these receptors. We found dramatically high mRNA expression and low protein production for a select set of proinflammatory cytokines including TNF and IL-6, as well as for the inflammasome proteins pro-IL-1 and NLRP3 in intestinal macrophages in comparison with bone marrow-derived and peritoneal macrophages. In contrast high mRNA but low protein production was not found for IL-10. Furthermore, activation of intestinal macrophages with TLR agonists resulted in upregulation of mRNA for NLRP3 and IL-1, but no increase in protein expression indicating a selective regulation of inflammatory genes at a post-transcriptional level. Furthermore, during experimental intestinal inflammation inflammatory monocytes and macrophages (CD64+F4/80+ cells) expressed high levels of both mRNA and protein for TNF, IL-1, and NLRP3 and produced high levels of IL-1 on activation of the NLRP3 and NLRC4 inflammasome indicating that microenvironmental signals during steady-state but not inflammatory conditions in the intestine control the expression of key inflammatory cytokines, including the NLRP3 and NLRC4 inflammasomes. Finally, blocking proteasome activity, as well as IL-10 signaling each resulted in enhanced production of NLRP3 and IL1 protein expression in intestinal macrophages from non-inflamed mice, suggesting novel mechanisms of post-

transcriptional control of inflammasome activation and proinflammatory cytokine production by intestinal macrophages.