GP2 is selectively expressed by small intestinal CD103+CD11b+ cDC

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affecting millions of patients worldwide. Studies showing strong associations between mucosal healing and increased patient survival point towards tissue repair as a target of novel therapeutic strategies. Using a mouse model of intestinal inflammation and repair (DSS-induced colitis), we performed an unbiased transcriptomic time-series analysis to identify novel potential therapeutical pathways related to mucosal healing. Briefly, we collected colonic tissues at different time points (from steady-state to inflammation to recovery) and processed them for RNA-seq, histology and FACS analysis. Transcriptional analysis on the differentially expressed genes identified 14 different expression patterns over time (clusters), among which 5 of them combined explain more than 65% of the variance observed in the experiment. Gene set enrichment analysis revealed that these 5 clusters contained mostly genes involved in cell migration, cytokine production, defence response to bacteria, angiogenesis and wound repair. FACS and histological analysis on the colon tissue corroborated the RNA-seq analysis, showing transient increase in neutrophil, T cell and monocyte recruitment at different time points and ultimately resulting in remodelling of tissue architecture towards repair. Surprisingly, processes such as cholesterol metabolism and RNA processing were also enriched concomitantly with the recovery phase, suggesting a potential role in inducing tissue regeneration. Altogether, time series analysis during intestinal inflammation suggests potential therapeutic targets that might influence mucosal healing after colonic inflammation.

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GP2 is selectively expressed by small intestinal CD103$^+$CD11b$^+$ cDC

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The functionality of tissue cDC is regulated, at least in part, by the signals these cells receive within their local environment. For example, we and others, have demonstrated that murine small intestinal but not colonic cDC are imprinted with an ability to generate the Vitamin A metabolite, retinoic acid, and thus an enhanced capacity to drive the generation of small intestinal homing T cells. Here we demonstrate that Glycoprotein 2 (GP2), a GPI-anchored protein previously shown to be selectively expressed by M-cells and to act as a receptor for type 1 fimbriated bacteria (1), is expressed by a large proportion of IRF4-dependent cDC in the small intestine but not in other tissues. While surface expression of GP2 by small intestinal CD103$^+$CD11b$^+$ cDC was independent of lymphocytes and MyD88 signaling, administration of broad spectrum antibiotics increased the proportion of GP2$^+$CD103$^+$CD11b$^+$ cDC in the small intestine. Moreover, GP2 expressing cDC in the small intestine were dramatically reduced in the setting of intestinal inflammation. We have previously shown that mice with an IRF4 deletion in CD11c$^+$ cells (Cd11c-cre.Irf4 $^{fl/fl}$ mice) have reduced numbers of small intestinal CD103$^+$CD11b$^+$ cDC (2). Interesting, we found that GP2$^+$ CD103$^+$CD11b$^+$ cDC were dramatically reduced in these mice. Finally, to address the in vivo role of GP2 expression by cDC, we have generated mice with a selective deletion of GP2 in CD103$^+$CD11b$^+$ cDC (huLangerin-cre.gp2 $^{fl/fl}$ mice). Results from these ongoing studies will be presented.

1. Hase K et al., Nature. 2009 Nov 12;462(7270):226–30
2. Persson EK et al., Immunity. 2013 May 23;38(5):958–69

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A novel saponin adjuvant G3 modulates cytokine responses in equine PBMC

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The applicability of a new saponin adjuvant formulation (G3) was tested in cultures of equine peripheral blood mononuclear cells (eqPBMCs). When immunizing mice with a split influenza vaccine the inclusion of this adjuvant could enhance the antibody response, as well as induce CD8$^+$CD3$^+$ T-cells and a broad protection against influenza challenge when a diterpene was incorporated in the G3 formula (van de Sandt et al., Vaccine. 2014 32: 5614–23.). Therefore, the present study aimed to evaluate cytokine responses to G3 alone or in combination with other immunostimulatory compounds. EqPBMC exposed to G3 for 18 h displayed an increased expression of the genes encoding IL-12p40 and IFN-γ (Th1), IL-23p19 (Th17), as well as IL-8 and IL-1β (pro-inflammatory). This G3-induced cytokine expression profile could be modified by co-culturing eqPBMC with G3 and known agonists to TLR5 (Flagellin) or TLR2/1 (Pam3CSK4). The combination of G3 with Pam3CSK4 increased the IFN-γ response compared to that induced by G3 or Pam3CSK4 alone. A similar increase in gene expression of IL-8 was indicated when G3 was combined with Flagellin. In contrast, the presence of G3 reduced the expression of the