Comparative transcriptional analysis of gut-associated regulatory factors on bone marrow-derived macrophages

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In the healthy gut, tissue-resident macrophages undertake various functions associated with maintaining normal gut physiology. These functions include those targeted at maintaining the epithelial barrier, such as apoptotic cell uptake and matrix remodelling, and those associated with neural activities, such as modulating peristalsis. To appropriately perform these functions macrophages must interpret a myriad of regulatory signals in the gut; failure to appropriately interpret these signals can lead to inflammation, as occurs in inflammatory bowel diseases (IBD). Currently, the precise impacts of different regulatory signals present in the gut environment on macrophage function is poorly understood. Moreover, the co-ordinated actions of these signals has not been explored. Here, we exposed bone marrow derived macrophages (BMDMs) to five candidate regulatory signals present in the gut and employed bulk RNA-seq to define their transcriptional effects. Our results demonstrate that BMDMs treated with three of the regulatory signals prostaglandin (PG)-E2, transforming growth factor (TGF)-β and IL-10 inhibit a shared module of inflammatory genes, including Tnfa and Il6. However, despite their common suppression of inflammatory cytokines, they each inhibited a distinct set of chemoattractant genes as well as expressing distinct combinations of genes implicated in gut homeostasis. Intriguingly, combinations of these factors, alongside retinoic acid (RA) and butyrate, had a stronger anti-inflammatory and pro-homeostatic effect than any factor individually. Taken together these data reveal that these factors may confer a shared anti-inflammatory state on macrophages, while promoting unique tissue homeostatic functions.

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