A gut microbiota-derived metabolite reroutes intestinal expansion of antigen presenting cells from circulating monocytes for enhancing anti-tumoral activity and survival in colorectal cancer.

BACKGROUND & AIMS: The intestinal mucosa inhabits the largest pool of phagocytes that fails to be constantly replenished from circulating monocytes in the absence of the gut microbiota. Understanding this paradigm is of importance as long-term compositional changes in the gut microbiome has been linked to the initiation and progression of neoplastic lesions even later in life. We herein investigated whether bacterial muramyl dipeptide (MDP), which occurs physiologically in high concentrations within the intestinal lumen, may interfere on the functional specialization of circulating monocytes into either dendritic cells (moDC) or macrophages (moMac) for intestinal homeostasis.
METHODS: The NOD2 gene expression levels of colorectal cancer patients was compared to outcome using databases. The transcriptomic data from NOD2hi and NOD2low tumors were further analysed for identifying gene pathways that were differentially enriched. We next performed cytometry and gene expression analysis by making use of the AOM/DSS model of mouse colorectal cancer. A mouse model of colitis and competitive bone-marrow chimera mice were used for evaluating the anti-inflammatory properties and the long-term autonomy of M-CSF-derived phagocytes from Nod2-deficient mice respectively. After these in vivo systems, we used in vitro culture approaches to study the impact of MDP on human monocytes differentiation into either dendritic cells or macrophages.
RESULTS: A shorter median survival time of patients was observed for those with the lowest transcript levels of NOD2. Such tumors were markedly characterized by a lowered expression of several genes involved in phagocytosis and antigen presentation. Conversely, the intratumoral abundance of monocyte-derived phagocytes was lowered in tumours from Nod2-deficient animals. qRT-PCR analysis further argued for a specific decrease in the accumulation of moDCs. This moDC shift was also found when treating human peripheral blood monocytes with MDP. Adoptive transfer of M-CSF-derived phagocytes alleviated the severity of DSS-induced colitis, while the absence of NOD2 gave a lowered advantage on the expansion of such cells as determined by competitive chimera experiment.
CONCLUSION: Herein, we identified a key role of the major Crohn’s disease predisposing NOD2 gene on the ontogeny of moDC that may account for the greater survival of colorectal patients with high levels of intratumoral NOD2.

Keywords : dendritic cell, macrophage, monocyte, NOD2, differentiation, tumor
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