Targeting nicotinamide phosphoryltransferase (NAMPT) in inflammatory bowel disease.

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Nicotinamide phosphoribosyltrasferase (NAMPT) is a pleiotropic protein essential for metabolism in mammalian cells. It is present in two different forms: an intracellular form, called iNAMPT and an extracellular form eNAMPT. iNAMPT catalyses the production of nicotinamide mononucleotide (NMN), precursor of NAD, therefore essential for the control of metabolism and ATP signalling (Chiarugi et al., 2012). The extra cellular form, eNAMPT, was first described as an active protein in the extracellular space and reported on its secretion from pre-B-cells and its ability to synergize with stem-cell factor and IL-7 to promote colony formation. Indeed, this was the basis of its classification as a cytokine, and demonstrated its biological potential as a putative paracrine and autocrine factor, however the mechanism of action is still unknown and only recently it has been proposed TLR4 as eNAMPT receptor. Importantly, iNAMPT and eNAMPT levels are increased in several pathologies, included inflammatory bowel disease (IBD). In particular, in ulcerative colitis (UC) the levels of NAMPT correlate with the stage of the pathology, indeed in an active state of the disease the level of NAMPT are very high, however its levels are partially reduced in a remission stage, indeed after three months of treatment, eNAMPT levels seem to be lowered (Moschen et al., 2007). The basis of the pathogenesis of UC is the dysregulation of normal immune survelliance, especially of immune adaptive response. In particular, in UC there is an unbalance of M1-polarized (pro-inflammatory) and M2-polarized (anti-inflammatory) macrophages, whith a predominace of the pro-inflammatory pool. Abundant inflammatory stimuli are able to cause iNAMPT over-expression and eNAMPT over-secretion, especially from innate immune cells such as neutrophils, monocytes, macrophages, epithelial and endothelial cells. The aim of our work was to determine the role of NAMPT and its inhibition in ulcerative colitis. First, we investigated if NAMPT could affect the macrophage polarization, using peritoneal macrophages as a model. We found that NAMPT mRNA levels are increased upon a pro-inflammatory stimulation (IFN and LPS), while Il-4, as an M2 stimulator, failed to evoke NAMPT expression. Moreover, also the stimulation with the eNAMPT sustains a M1 polarization state of the macrophages, prompt NAMPT as a crucial cytokine in maintaining the inflammatory state. In order to unravel the role of NAMPT in ulcerative colitis, we used NAMPT inhibitors (e.g. FK866; MV87) in two mouse models of acute colitis: DSS model and DNBS model. As expected, we found that intracellular and extracellular NAMPT are increased in colon tissue and serum of DSS and DNBS mice compared to control (sham operated mice), and more important the levels of NAMPT are reduced after the treatment with NAMPT inhibitors. Furthermore, the treatment with NAMPT inhibitors reduced the body weight loss, the colon length shortening and the damage of colon tissue (determined by HeE staining), at similar levels compare to the current pharmacological treatment (Travelli et al., 2017) Taken together, our data support the fact that NAMPT, by sustain the inflammatory state, is a biomarker for UC, and could be a druggable target in this pathology.

Chiarugi et al., (2012) Nat Rev Cancer, 12:741-52

Moschen et al., (2007) The Journal of Immunology 178:1748-1758

Travelli et al., (2017) J Med Chem, 60(5):1768-1792