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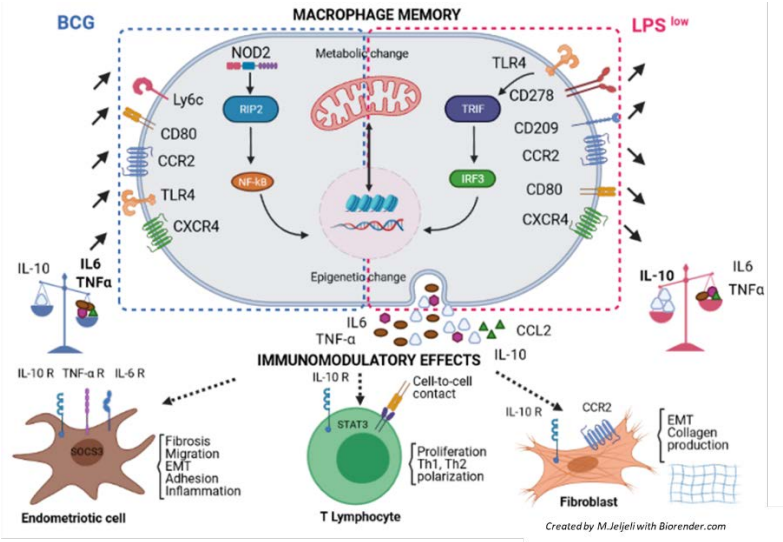

"Trained immunity" and role of macrophage memory in the immunomodulation of fibro-inflammatory diseases

Fibro-inflammatory diseases are pathologies that affect various organs such as the skin, the liver, the lungs, and the digestive system and thus are life-threatening. Despite a wide etiological spectrum of infectious, toxic or immunological causes, the dysregulation of the innate immune response with an exacerbation and maintenance of the inflammatory process remains the major element of their pathogenesis. Recently, it has been shown that specific innate immune cells such as macrophages can acquire a type of rudimentary immunological memory following a first antigenic exposure and can react differently to a second stimulation, with either a heightened inflammatory response or an anergic/anti-inflammatory status, depending on the type of the first antigen encountered.

In this work, we support the reasoning that such memory induction in macrophages can affect the course of the inflammatory process and therefore can influence the proliferation of tissue fibrosis.

We first show that macrophages' *in vivo* and *in vitro* pre-stimulation with BCG or LPS at low repeated doses (LPS^{low}) induces singular phenotypic, metabolic, and epigenetic modifications and confer them opposite functional properties. *In vivo* stimulation with LPS^{low} alleviates early inflammation and chronic fibrosis in the mouse model of HOCl-induced systemic sclerosis (SSc), while BCG exacerbates it. The adoptive transfer of LPS^{low} or BCG memory macrophages can also have either beneficial or aggravating effects, respectively. Additionally, co-culture with LPS^{low} memory macrophages reduces the fibro-inflammatory profile of myofibroblasts in mice and SSc patients with a cytokinic deviation towards an excess of IL-10. This immunomodulatory effect is found in the murine model of endometriosis (EDT) characterized by a chronic inflammation associated with the implantation of ectopic endometrial lesions. Along with the volume and glandular activity reduction of endometriotic lesions, *in vivo* stimulation of EDT mice with LPS^{low} leads to an expression decrease of costimulatory molecules and chemokine receptors of peritoneal macrophages, as well as a hypo-production of pro-inflammatory cytokines. The co-culture of LPS^{low} memory macrophages with human endometriotic cells induces a decrease in markers of fibrosis, adhesion, and cell migration molecules, but an increase in STAT3 phosphorylation and the expression of Socs3 and Bcl3, target genes of the IL-10 cytokine. This effect, abrogated by the coculture with the siRNA-IL10 or the pSTAT3, demonstrates the IL-10 dependent anti-inflammatory and anti-fibrotic mechanism. LPS^{low} macrophages are also able to modulate the allogeneic response *in vitro* in a mixed lymphocyte reaction and *in vivo* in the mouse model of Graft-versus-Host Disease via decrease of the initial inflammation responsible for triggering and maintaining the allogenic immune process. This effect is associated with an increase of IL-10 production, a decrease in the synthesis of TNF-α, IFN-γ, IL-6, a change in the chemokine networks and their receptors, and a reduction in the memory lymphocyte phenotype leading to a significant drop in organs damage and mortality rate. Finally, we demonstrate that the adoptive transfer of LPS^{low} macrophages does not worsen the growth of murine B lymphoma A20 tumor cells, unlike BCG macrophages that slow tumor proliferation by promoting the production of TNF-α and IL-6, $CD4^+$ and $CD8^+$ T cell activation, and the expression of inflammation-associated genes at the splenic and tumor level.

Consequently, this work demonstrates that prior antigenic macrophage stimulation induces a memory phenotype that can be expressed in case of a fibro-inflammatory disease and either alleviates or worsens its clinical and biological presentation via the modulation of the inflammation pathways and the adaptive immune cells activation.