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Inflammation in tuberculosis: interactions, imbalances and interventions

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Inflammation is critical for tuberculosis (TB) pathogenesis. The nonresolving aspect of inflammation in TB is caused by sophisticated intracellular survival strategies of tubercle bacilli. TB is a continuum comprising a spectrum of lesions as a consequence of complex regulation of inflammation. Proinflammatory cytokines, including interferons, tumor necrosis factor and interleukin 1 along with microRNAs and eicosanoids form an interactive network during TB. Cross-regulation between proinflammatory mediators strongly impacts on infected cell death patterns. These processes, in concert with local concentrations of proteases, such as cathepsins, serpins and matrix-metalloproteinases, affect tissue integrity, shape the architecture of granulomas and modulate tissue repair. With inflammation networks being uncovered in TB, the relevance of several pathways for novel interventions becomes clearer.

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Introduction

Inflammation is not only fundamental to the maintenance of homeostasis but also life preserving [1,2]. This biological process is tightly controlled at different levels and new key molecular regulators of inflammation have been characterized recently [3]. Dysregulated inflammation represents a central pathogenic feature of numerous life-threatening microbial infections, including tuberculosis (TB) [4]. For millennia, TB has been a major threat to humankind. It is a local disease, typically focused on the lung, which serves as both port of entry and site of disease manifestation in ca. 80% of all cases. The disease is caused by a highly robust and sophisticated bacterial pathogen, *Mycobacterium tuberculosis* (*Mtb*), which resists and even subverts protective immunity. The success of this strategy is reflected by the epidemiology of the disease: 2 billion individuals are infected with *Mtb*. These latently TB infected individuals (LTBI) actively contain the pathogen but fail to eradicate it, thus serving as reservoir for active disease which develops in 9 million cases annually. During latency, *Mtb* persists in a dormant stage over long periods of time without damage or transmission. However, once the equilibrium between *Mtb* and immune system becomes dysbalanced, *Mtb* is resuscitated to a metabolically active and replicative stage and grows to numbers exceeding billions of organisms. This exuberant bacterial load causes damage to the host and allows transmission.

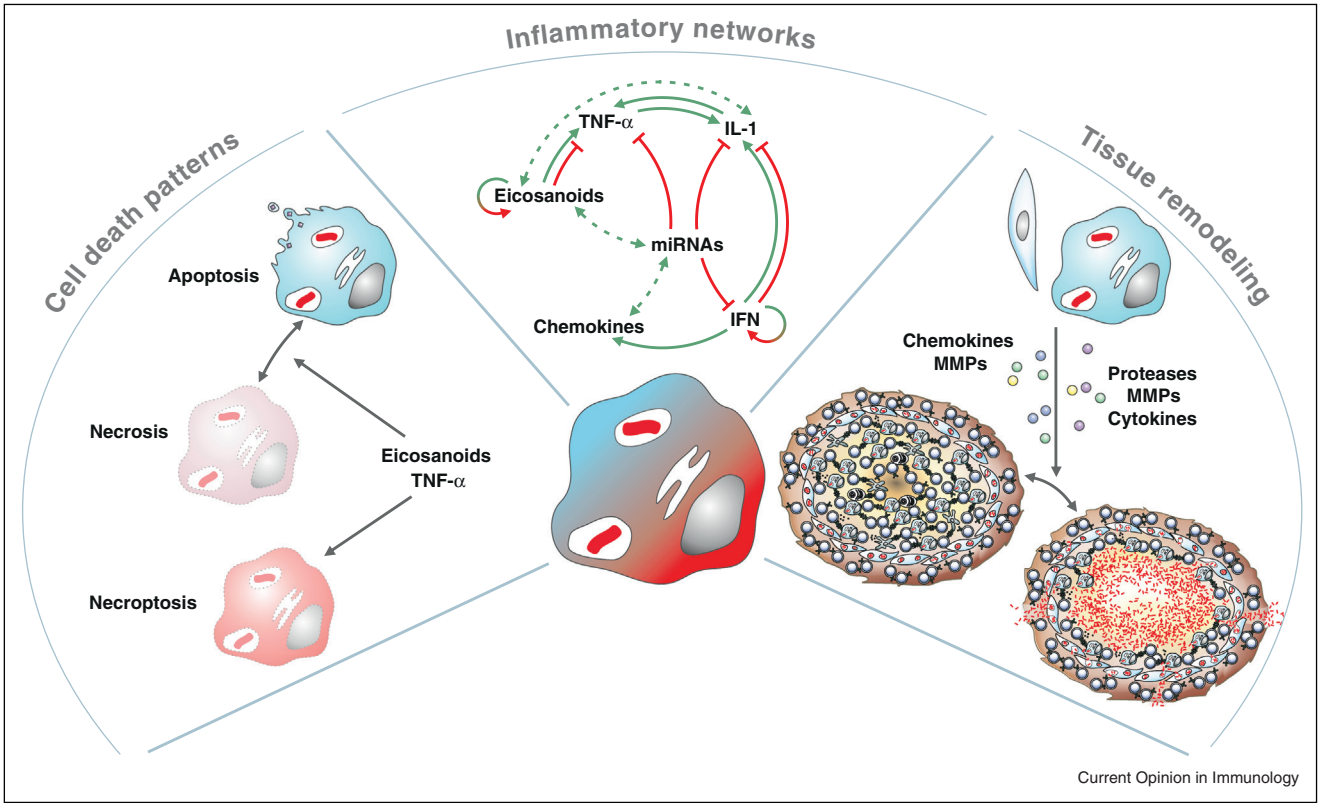
Dissociation of infection from disease is highly intriguing from an immunologic standpoint. During latent infection, the immune system contains the pathogen by means of controlled inflammation causing minimal collateral damage. Nonetheless, TB is characterized by nonresolving inflammation both during latency and active disease. *Mtb* likely co-evolved with the eukaryotic host and particularly the macrophage to take advantage of the inflammatory process in multiple ways. During this interplay firstly, a silent and protracted infection evolves; secondly, immunologic tissue reactions occur and granulomas develop to contain *Mtb* but also to allow its persistence; and thirdly, immunity rearranges between LTBI and active infection. We will discuss novel insights into inflammation in TB, how *Mtb* manipulates inflammation and describe recent advances towards intervention against TB which target inflammation. We conclude our review with a brief update of recent advances from the clinical front.

Molecular regulation of TB inflammation

Mtb is endowed with the unique capacity to modulate fundamental inflammatory processes, such as recruitment of immune cells to the infected lung and production of critical proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1 and interferons (IFN). In addition, the bacilli interfere with biochemical pathways relevant to production of eicosanoids and other lipid mediators with reparatory functions. These molecular events appear to be highly interconnected in TB and skewed to the benefit of *Mtb* (Figure 1).

Tissue recruitment of inflammatory cells is orchestrated by chemokines. These mediators as well as their receptors have caught increasing attention by TB immunologists. *Mtb* triggers a unique temporal regulation of

Figure 1



Multiple layers of regulation of inflammation in TB. **Central panel**: interactions of *M. tuberculosis* (*Mtb*) with professional phagocytes results in activation of several pathways, which concur to induce inflammation. IL-1 necessitates differential requirement for caspase-1 and subsequently inflammasome activation in infected myeloid cells. Inflammasomes, particularly NLRP3, are indispensable for bioactive IL-1β release and these platforms are regulated by interferons (IFN) via negative (iNOS/NO and IL-10) and positive loops (GBP5). IL-1 affects TNF-α synthesis and TNFR expression, while *Mtb* impacts directly or via distinct eicosanoids on TNF-α abundance (LTB4 boosts and LXA4 dampens TNF-α release). MiRNAs perturb TNF-α as well as IFN-γ post-transcriptionally and perhaps affect other mediators (IL-1, chemokines). Eicosanoids (PGE2 and LXA) and IFN (type I and II) crosstalk with family members and probably additional networks exist between these molecules and the above-mentioned mediators. **Left panel**: distinct proteinaceous and lipid mediators impact on the fate of the infected cell. Eicosanoids direct cell death (apoptosis vs. necrosis), while abundant TNF-α favors necroptosis and hyper-inflammation. **Right panel**: genesis of nascent granulomas is controlled by immune and nonimmune cells via chemokines and cytokines. Local abundance of proteases (serpins, cathepsins) and cytokines regulate transition of solid granulomas to necrotic ones. In addition matrix-metalloproteases, of myeloid or epithelial origin, modulate the extent of tissue damage. Hypo- or hyper-reactions alter inflammation and, along with *Mtb* persistence, transform a physiological process into a life-threatening condition. GBP5: guanylate binding protein 5; iNOS: inducible nitric oxide synthase; IFN-γ: interferon gamma; IL-1: interleukin 1; IL-10: interleukin 10; LTB4: leukotriene B4; LXA4: lipoxin A4; miRNAs: microRNAs; PGE2: prostaglandin E2; TNF-α: tumor necrosis factor alpha.

chemokines in the lung [5]. CCR2/CCR5 and CXCR1/CXCR2 ligands are promptly released after *Mtb* encounter to attract phagocytes, whilst CXCR3, CCR5 and CCR6 ligands modulate accumulation of T and B lymphocytes thereafter. CXCR1-binding and CXCR2-binding chemokines appear to be secreted not only by myeloid cells, but also by lung-resident nonhematopoietic cells. Production of the neutrophil-recruiting chemokine CXCL8 by lung fibroblasts has been reported in TB [6] and pneumocytes produce this chemokine when stimulated with *Mtb* [7]. Given the abundance and physiological relevance of respiratory epithelia for lung function these cells are likely more than quiet bystanders. Rather, they act as central coordinators of a first line of defence executed by leukocytes, newly attracted to the lung promptly after first encounter with *Mtb*. Later, during infection, CXC chemokines regulate granuloma formation and adaptive immune responses. These aspects were reiterated by recent studies. CXCL13-driven accumulation of $CD4^{+}CXCR5^{+}$ T cells during TB has substantial consequences for disease outcome [8]. This chemokine drives recruitment of responder T cells into ectopic lymphoid structures associated with lung granulomas for proper macrophage activation. It will be of interest to investigate in how far regulation of CXC chemokines, either early postexposure with *Mtb* or subsequent to activation of adaptive immunity, follows not only a timely but also a spatial pattern.