Type I interferon signaling and macrophages: a double-edged sword?

Barbara Adler [1] and Heiko Adler [2*]

[1] Max von Pettenkofer Institute & Gene Center, Virology, Faculty of Medicine, LMU München, Munich, 81377, Germany

[2] Research Unit Lung Repair and Regeneration, Comprehensive Pneumology Center, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH); Member of the German Center of Lung Research (DZL), Munich, Germany

* Correspondence: Heiko Adler (h.adler@helmholtz-muenchen.de)

In a recent issue of the Journal of Experimental Medicine, Zhang et al. report that type I interferon (type I IFN) signaling mediates Mycobacterium tuberculosis (Mtb)-induced macrophage (MΦ) death, most likely by a new, currently unknown cell death pathway [1].

Type I IFNs are a major host defense against viral and bacterial infections. They are produced by a variety of cell types including MΦ. After recognition of pathogen-associated molecular patterns (PAMPs) by, for example, Toll-like receptors (TLRs), host cells produce type I IFNs that can act in both autocrine and paracrine ways to activate or repress IFN-stimulated genes (ISGs) [2;3]. Besides interfering with multiple stages in the life cycle of pathogens, type I IFNs have additional functions influencing both innate and adaptive immune responses, which can result in beneficial but also detrimental effects in the host (Fig. 1). It seems that the outcome of the type I IFN response is highly context dependent [3]. For example, type I IFN signaling during bacterial infections is dependent on many factors, e.g. whether the bacteria are intra- or extracellular, thereby activating different signaling pathways. While type I IFN signaling is crucial for host defense against some bacteria, e.g. pneumococci, it may promote infection by others including Mtb [3;4]. Mtb infects MΦ, and once inside the cell, it inhibits the development of phagosomes to phagolysosomes, enabling Mtb not only to survive but also to replicate. Infected MΦ will eventually die, releasing bacteria spreading to more cells. Thus, Mtb-induced MΦ death is a crucial factor in the pathogenesis of tuberculosis. Despite this importance of Mtb-induced MΦ death, the mechanism behind remained elusive so far.

Therefore, Zhang et al. [1] set out to investigate by which type of cell death the Mtb-infected MΦ die. Surprisingly, they discovered that the hitherto known types of cell death are obviously not involved. Specifically, by using a variety of approaches, e.g. the application of inhibitors of specific cell death pathways and knockout cells, they excluded apoptosis, pyroptosis, necroptosis, parthanatos, ferroptosis,

and autophagy-dependent cell death. From these data, the authors concluded that Mtb-induced MΦ death might involve a novel mechanism. To identify this mechanism, the authors performed a genome-wide CRISPR-Cas9 screen in an Mtb-infected MΦ cell line. This screen identified type I IFN signaling as important for the death of Mtb-infected MΦ. Subsequent genetic and immunological studies confirmed that autocrine and paracrine type I IFN signaling plays an important role in the death of Mtb-infected MΦ. Crucially, the authors went on to demonstrate that blocking type I IFN signaling protects Mtb-infected mice and, importantly, augmented the benefit of rifampin, a medication used to treat drug-sensitive tuberculosis.

For tuberculosis, the connection that type I IFN signaling is detrimental to the host by promoting MΦ death and propagation of Mtb from those dead MΦ is new. For Salmonella typhimurium, type I IFN signaling had already been implicated in MΦ death during infection [5]. In this case, it induces MΦ necroptosis, resulting in a reduced control of infection. During Listeria infection, type I IFN promotes apoptotic MΦ cell death, leading to innate immune suppression [6]. Type I IFN-induced MΦ cell death must not necessarily be direct. More than two decades ago, we described that IFN-α can prime MΦ for activation-induced apoptosis [7]. Exposure of MΦ to recombinant or herpesvirus-induced IFN-α, followed by activation with lipopolysaccharide (LPS), induced MΦ apoptosis. We suggested that this pathway might contribute to the pathogenesis of diseases. Indeed, we found that MΦ infected with the cytopathic biotype of bovine viral diarrhea virus (BVDV) produced factors, including type I IFN, which primed both infected and uninfected MΦ for LPS-induced apoptosis. Considering that the principal lesions of mucosal disease, the lethal form of infection with cytopathic BVDV, are located in regions with high concentrations of endotoxin (oral cavity and gastrointestinal tract), our findings strongly suggested a role of this pathway in the pathogenesis of mucosal disease [8].

By showing a key role for type I IFN signaling in Mtb-induced MΦ cell death, Zhang et al. [1] uncovered a new mechanism for adverse effects of pathogen-induced type I IFN on disease outcome. Furthermore, they suggest that the MΦ cell death happens via a new, so far unknown cell death pathway. Type I IFN-dependent MΦ cell death thus results in release of bacteria from infected MΦ, securing Mtb spread, and very likely in release of factors that trigger inflammation and tissue damage. The latter might be particularly relevant in the lung, where a balance between protective and pathological immune responses is highly important to minimize immunopathology and maintain pulmonary function [9]. The findings of Zhang et al. suggest that blockade of type I IFN signaling might be a new therapeutic avenue for the treatment of tuberculosis. In particular, and as they already showed in a mouse model, blocking type I IFN signaling could perhaps be applied as addition to the treatment with antibiotics. Thus, the development of new treatment strategies will be a future research path. In addition, the new, unknown cell death pathway and its underlying mechanism warrants further studies. Overall, the findings of Zhang et al. may not only be important for tuberculosis but for the pathogenesis of bacterial - and perhaps also some viral - infections in general. Elucidating the details of type I IFN signaling in MΦ cell death might lead to new host-directed therapies of a variety of diseases.

FIGURE LEGENDS

Figure 1: Infected macrophages produce type I interferon that, by autocrine and paracrine signaling, may exert antimicrobial effects, contributing to host defense and protection, or induce macrophage death, potentially leading to pathology and disease. The final outcome is most likely context-dependent, i.e., for example determined by pathogen type, infection dose, host genetics and target organ.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

89

90 **REFERENCES**

91 1. Zhang L, Jiang X, Pfau D, Ling Y, Nathan CF. Type I interferon signaling mediates Mycobacterium
92 tuberculosis-induced macrophage death. J.Exp.Med. 2021;218:e20200887.

93 2. Odorizzi PM, Wherry EJ. An interferon paradox. Science. 2013;340:155-156.

94 3. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease.
95 Nat.Rev.Immunol. 2015;15:87-103.

96 4. Snyder DT, Hedges JF, Jutila MA. Getting "Inside" Type I IFNs: Type I IFNs in Intracellular Bacterial
97 Infections. J.Immunol.Res. 2017;2017:9361802. doi: 10.1155/2017/9361802. Epub 2017 Apr
98 26.:9361802.

99 5. Robinson N, McComb S, Mulligan R et al. Type I interferon induces necroptosis in macrophages during
100 infection with Salmonella enterica serovar Typhimurium. Nat.Immunol. 2012;13:954-962.

101 6. Carrero JA. Confounding roles for type I interferons during bacterial and viral pathogenesis.
102 Int.Immunol. 2013;25:663-669.

103 7. Adler B, Adler H, Jungi TW, Peterhans E. Interferon-α primes macrophages for lipopolysaccharide-
104 induced apoptosis. Biochem.Biophys.Res.Comm. 1995;215:921-927.

105 8. Adler B, Adler H, Pfister H, Jungi TW, Peterhans E. Macrophages infected with cytopathic bovine viral
106 diarrhea virus release a factor(s) capable of priming uninfected macrophages for activation-induced
107 apoptosis. J.Virol. 1997;71:3255-3258.

108 9. Divangahi M, King IL, Pernet E. Alveolar macrophages and type I IFN in airway homeostasis and
109 immunity. Trends Immunol. 2015;36:307-314.

110

Type I interferon and macrophages