Putting the p(hosphor) in pyroptosis

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A recent study in Science found Mycobacterium tuberculosis inhibits pyroptosis of the host cell by secreting a phosphatase (PtpB). PtpB targets the plasma membrane to dephosphorylate PI4P and PI(4,5)P2, inhibiting recruitment of the pore-forming gasdermin D N-terminal fragment. Pyroptosis inhibition contributes to virulence, as ptpB-deficient Mtb is attenuated in mice.

Inflammasomes are multi-protein complexes designed to recognize cytosolic danger/pathogen-associated molecular patterns (D/PAMPs) and activate the innate immune system. Two well-studied sensor components of inflammasome complexes are AIM2, which binds to double-stranded DNA, and NLRP3, which senses intracellular DAMPs (Figure 1).1 Activated NLRP3 or AIM2 bind to the adaptor protein ASC for subsequent recruitment and autoactivation of the zymogen protease, pro-caspase-1 (Figure 1).1 A major consequence of inflammasome-activated caspase-1 is the cleavage of latent, immature forms of unconventional secreted cytokines, such as pro-IL1β, and gasdermin D (GSDMD) to generate an N-terminal fragment (GSDMD-NT) that forms pores in the plasma membrane (PM) through which mature IL-1β is secreted. These events can ultimately lead to the rupture of the PM via NINJ1 oligomers in an inflammatory death process termed pyroptosis (Figure 1).7

Mycobacterium tuberculosis (Mtb) is a strict human pathogen that constitutes a major burden on global public health.5 Prior reports demonstrate that, depending on time and context, IL-1β has a protective role in host defense against Mtb in humans and the mouse model of tuberculosis.10 It is thus counterintuitive that the deletion of mouse inflammasome components important for the activation of the inflammasome complex, such as the adaptor protein ASC, have no significant effect on host resistance after Mtb infection.5 These data could be interpreted as an absence of function of inflammasome complexes for host protection. Alternatively, one could propose that, being a highly host-adapted pathogen, Mtb has evolved ways to inhibit host cell inflammasome recognition and/or activation and that, therefore, creating inflammasome-response-deficient mice does not make a difference to the host response anymore. Evidence in support...
of this hypothesis is that Mtb expresses several proteins that are involved in inhibiting host cell inflammasome activation (Figure 1).² Hip1 of Mtb limits host cell TLR-2 signaling, which may inhibit typical signal 1 transcriptional and non-transcriptional “priming” events prior to inflammasome triggering.² Moreover, Rv3364c indirectly inhibits caspase-1 activation,² and Mtb PknF inhibits NLRP3 activation (Figure 1).³ Mtb also inhibits the AIM2 inflammasome upstream of inflammasome complex formation via an unknown mechanism (Figure 1).⁴ Adding to the compendium of bacterial strategies to hide from and inhibit inflammasome signaling, a recent study from Chai et al. in Science now adds several Mtb proteins (Rv0153c/PtpB, Rv0561c, Rv0824c/DesA1, Rv0861c/Ercc3, Rv1515c, and Rv1679/FadE16) as putative effectors that limit IL-1β secretion and pyroptosis.⁵ The authors performed an elegant screen based on the capacity of a protein out of 201 screened Mtb proteins to suppress inflammasome activation and, more precisely, IL-1β secretion in model HEK293T cells.⁶ Chai et al. created a mutant that activates pyroptosis more strongly by deleting the phosphatase B (ptpB) in Mtb and demonstrate that this mutant (ΔptpB Mtb) is attenuated in mice. Importantly, the attenuated phenotype of the deletion mutant is dependent on the presence of the host cell inflammasome substrate GSDMD, which is the target of PtpB since in gsdmd⁻/⁻ mice, wild-type Mtb and ΔptpB Mtb have the same virulence. These data support a model in which host cell inflammasome activation can mediate a protective response, but Mtb may inhibit inflammasome activities, namely GSDMD pore formation, to promote virulence. The mechanisms of the protective host inflammasome-dependent immune response in the context of Mtb infections will be of interest in future studies and may help to establish correlates of

Figure 1. Mycobacterial effectors inhibit different steps of the inflammasome signaling pathway

Several Mtb effectors either secreted (PtpB or Rv3364c) or non-secreted (Hip-1 or PknF, as indicated by *) are involved in evasion of inflammasome-mediated secretion of pro-inflammatory cytokines and pyroptosis. Unknown Mtb effectors are represented by ?. Both PtpA and PtpB are activated by binding of host ubiquitin to a UIM-like domain. In contrast to PtpA, once activated, PtpB localizes to specific PM lipids PI4P and PI(4,5)P2, thereby dephosphorylating PI, and thus inhibits the binding and membrane localization of activated GSDMD-NT fragment. Dashed lines, indirect interaction; solid lines, direct interaction; arrowhead, activation; blunt end, inhibition. TLR2, toll-like receptor 2; NF-κB, nuclear factor kappa B; PtpA, protein tyrosine phosphatase A; PtpB, protein tyrosine phosphatase B; PM, plasma membrane; Ub, ubiquitin; UIM, ubiquitin-interacting motif; TRIM27, tripartite motif-containing protein 27; JNK, Jun N-terminal kinase; PknF, protein kinase F; NLRP3, nucleotide-binding domain (NOD)-like receptor protein 3; AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; NT- GSDMD, N-terminal gasdermin D fragment; P14P, phosphatidylinositol 4 phosphate; PI(4,5)P2, phosphatidylinositol 4,5 bisphosphate; PI, phosphatidylinositol; PS, phosphatidylserine; PE, phosphatidylethanolamine; PC, phosphatidylcholine; SM, sphingomyelin; GSL, glycosphingolipids. Created with https://biorender.com/
...that await further investigation for PI4P. There are other compelling organelles that can target other organelles is of inter-...cleavage by a bacterial phosphatase from Mtb, but this may suggest that this mechanism guarantees that the host does not allow the pathogen to localize to the nucleus.

Another intriguing question remaining to be answered is the nature of the host cell ubiquitination system that targets PtpB? Finally, why are the PtpA/B phosphatase activities dependent on host cell ubiquitination? One hypothesis is that this mechanism guarantees that the phosphatases are only active when localized in the host cell cytosol, which might be of advantage if, for example, targeting PI4P/PI(4,5)P2 on the luminal side of the phagosomal membrane is of a disadvantage to the pathogen.

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