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Commentary

Calcium & ROS: Two orchestra directors for the requiem of death

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ABSTRACT

Tumor necrosis factor alpha (TNF) triggers regulated necrosis of mycobacterium-infected macrophages through of mitochondrial reactive oxygen species (mitoROS) production in a RIPK1/3-dependent manner. To explain that, Roca and colleagues describe an inter-orgallenar circuit which involves the lysosomal ceramide production, mitoROS, BAX activation and RyR Ca^{2+} efflux from the endoplasmic reticulum into the mitochondrion.

TNF is a master pro-inflammatory cytokine with important functions in physiological homeostasis and disease pathogenesis. TNF generates a wide range of responses through the binding to and activation of both TNF receptor 1 (TNFR1) and TNFR2. TNFR1 is expressed ubiquitously and promotes inflammation and cell death, whereas TNFR2 expression is restricted to some specific cell types and induces cell survival and tissue regeneration. Moreover, the TNFR1 activation can sensitize cells to either RIPK1-independent apoptosis, RIPK1-dependent apoptosis or necroptosis, which is mediated by the necrosome, a complex form by RIPK1, RIPK3 and MLKL [1]. These pleiotropic responses induced by TNF have stimulated the development of therapies focused on blocking the TNF signal. Despite improving of the quality of life of millions of patients affected by TNF-associated disease [2], anti-TNF therapy has turned out to be a risk factor for reactivation of latent tuberculosis (TB) [3], an unexpected side effect. According to Word Health Organization, TB due to *Mycobacterium tuberculosis* (Mtb) infection is still one of the top 10 causes of death worldwide.

An important Mtb pathogenic variable could be the induction of any necrotic cell death, promoting further cell death and inflammation. To explain how TNF response causes regulated necrosis of mycobacterium-infected macrophages, Roca et al. [4] described an interesting inter-organellar circuit which begins and leave off in the mitochondria to explain how TNF signaling causes regulated necrosis of the mycobacterium-infected macrophages. This circuit begins when TNF and Mtb infection stimulate mitoROS production in a RIPK-1 and RIPK3-dependent manner. mitoROS induces lysosomal ceramide synthesis, leading to BiD and BAX activation. However, BAX activation does not lead to the induction of a canonical apoptosis. Roca and colleagues proposed that BAX localizes to the endoplasmic reticulum (ER) to stimulate the ryanodine receptors (RyR), which mediate Ca^{2+} efflux from the ER toward the mitochondrion. Then, the resultant mitochondrial Ca^{2+} overload triggers cyclophilin-D-mediated necrosis and the circuit is completed (Fig. 1A). This inter-organellar circuit described by Roca et al. [4] is observed in several cell types and cellular processes including metabolism, energy production and cell death. In fact, multiple organelle types simultaneously interact with mitochondria, being the ER the most prominent interacting partner, followed by the Golgi apparatus [5]. Despite contacts between mitochondria and lysosomes remains poorly studied, it has been described that they can regulate mitochondrial fission and lysosomal dynamic [6]. Interestingly, the authors described for a first time the role of BAX for RyR regulation. Although the mechanism remains indeterminate, they demonstrated that BAX-dependent activation of RyRs was independent of its BH3 domain, which is required for its oligomerization. Moreover, this effect depends on BAX localization to the ER. Contrary to the effect of BAX on the RYR channel, the anti-apoptotic protein BCL-2 directly inhibits RyR-mediated Ca^{2+} release, through its BH4 domain [7] (Fig. 1B). Moreover, the scenario becomes even more complex, because others ER-calcium regulators also affects regulated necrosis. TMBIM3 and TMBIM6 are two components of TMBIM-protein family and have emergent role in cell death [8]. Both antiapoptotic proteins TMBIM3 and TMBIM6 also inhibit TNF-mediated mitochondrial Ca^{2+} and regulated necrosis. However, it remains to be deciphered whether the interaction between RyR and BCL-2 can be modulated by the

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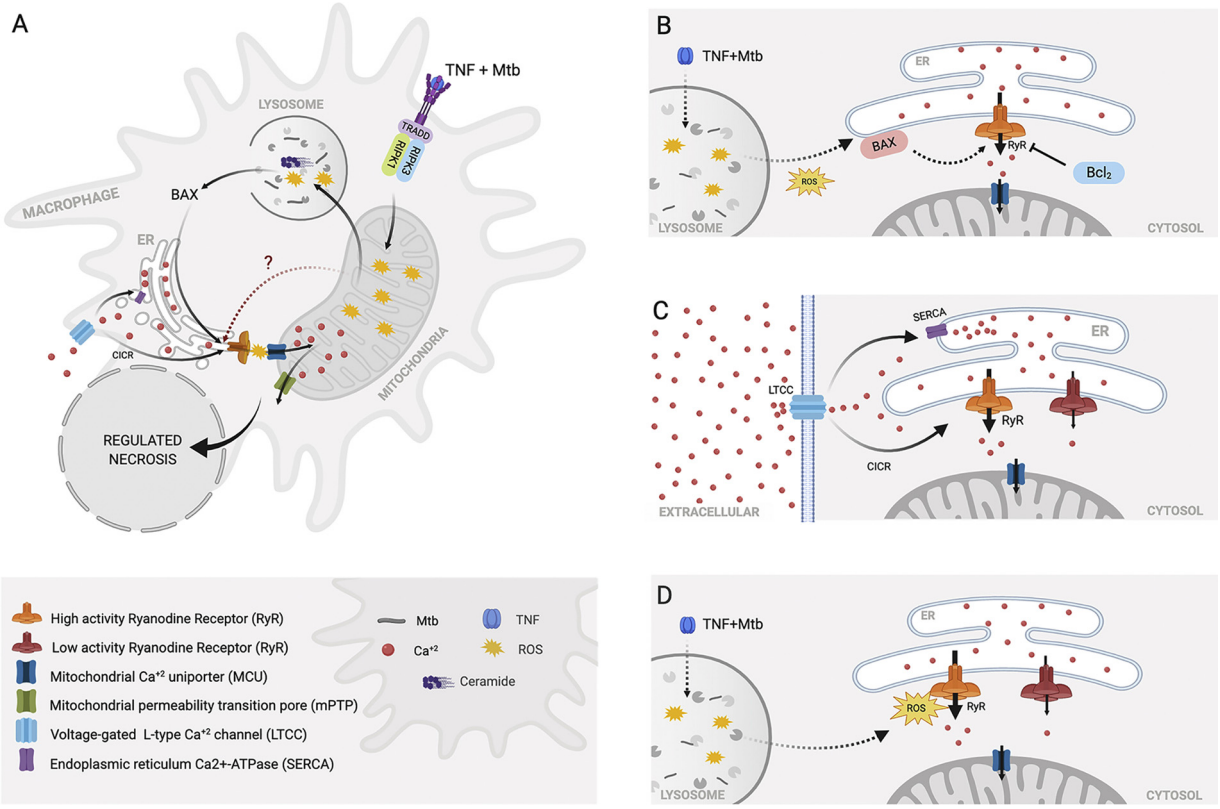

Fig. 1. RyR-mediated Ca^{2+} signals in TNF-induced necrosis of mycobacterium-infected macrophages. A) Scheme of inter-organellar circuit of TNF-mediated macrophage necrosis pathway. B) BAX promotes RyR-mediated Ca^{2+} release from de ER to into de mitochondria. In the opposite way, BCL-2 directly inhibits RyR-mediated Ca^{2+} release, through its BH4 domain C) LTCCs-mediated Ca^{2+} signal promotes amplification and propagation of RyR-mediated Ca^{2+} release by CICR. D) mitoROS changes the cellular redox state promoting the oxidation of RyR-cytoplasmic cysteine residues leading to the activation of RyR channel.

stoichiometric equilibrium between BCL2 and BAX, which is a key point on apoptosis regulation, as well as by the expression levels of TMBIM3 and TMBIM6.

Additionally, pharmacological evidence showed that voltage-gated L-type Ca^{2+} channels (LTCCs) also are involved in TNF-mediated mitoROS and Ca^{2+} levels, as well as regulated necrosis [4]. Roca et al. proposed that mitoROS stimulates the production of lysosomal ceramide starting the inter-organellar circuit in the Mtb-infected macrophages model. However, it could be also possible that both LTCCs-dependent Ca^{2+} and mitoROS can directly regulate RyR-mediated Ca^{2+} release and programmed necrosis. Ca^{2+} is the physiological agonist of RyR that triggers Ca^{2+} release from ER, participating in Ca^{2+} -induced Ca^{2+} release (CICR), a conserved cellular mechanism that allows amplification and propagation of the Ca^{2+} signals initially generated by Ca^{2+} entry from the extracellular space (Fig. 1C). Moreover, RyR channels can act as intracellular redox sensors due to possessing cysteine residues in the cytoplasmic domain, which are highly susceptible to oxidative modifications, with remarkable effects on RyR function (Fig. 1D). Increasing RyR-cysteine oxidation enhances channel activity as well as the sensitivity to activation by Ca^{2+} [9]. These evidences suggest that LTCCs-dependent Ca^{2+} stimulates RyR by CICR increasing the RyR-mediated Ca^{2+} release and macrophages death. While the mitoROS production (induced by TNF in infected macrophages through RIPK1-RIPK3-dependent pathways) could generate H_2O_2 enriched nanodomain at the interaction site between ER and mitochondria [10], stimulating RyR activity, with the consequence TNF-exacerbated response. Thus, the orchestrated regulation of RyRs mediated by BAX, ROS and Ca^{2+} signaling can fine-tune the crosstalk between the ER and mitochondria to control mitochondrial Ca^{2+} overload in Mtb-infected macrophages.

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References

[1] J. Yuan, P. Amin, D. Ofengeim, Necroptosis and RIPK1-mediated neuroinflammation in CNS diseases, Nat. Rev. Neurosci. 20 (2019) 19–33, https://doi.org/10.1038/s41583-018-0093-1.
[2] G.D. Kalliolias, L.B. Ivashkiv, TNF biology, pathogenic mechanisms and emerging therapeutic strategies, Nat. Rev. Rheumatol. 12 (2016) 49–62, https://doi.org/10.1038/nrrheum.2015.169.
[3] M. Pai, M.A. Behr, D. Dowdy, K. Dheda, M. Divangahi, C.C. Boehme, A. Ginsberg, S. Swaminathan, M. Spigelman, H. Getahun, D. Menzies, M. Raviglione, Primer on tuberculosis, Nat. Rev. Dis. Prim. 2 (2016), https://doi.org/10.1038/nrdp.2016.76.
[4] F.J. Roca, L.J. Whitworth, S. Redmond, A.A. Jones, L. Ramakrishnan, TNF induces pathogenic programmed macrophage necrosis in tuberculosis through a mitochondrial-lysosomal-endoplasmic reticulum circuit, Cell 178 (2019) 1344–1361, https://doi.org/10.1016/j.cell.2019.08.004 e11.
[5] A.M. Valm, S. Cohen, W.R. Legant, J. Melunis, U. Hershberg, E. Wait, A.R. Cohen, M.W. Davidson, E. Betzig, J. Lippincott-Schwartz, Applying systems-level spectral imaging and analysis to reveal the organelle interactome, Nature 546 (2017) 162–167, https://doi.org/10.1038/nature22369.
[6] I. Gordaliza-Alaguero, C. Cantó, A. Zorzano, Metabolic implications of organelle–mitochondria communication, EMBO Rep. 20 (2019), https://doi.org/10.15252/embr.201947928.
[7] T. Vervliet, J.B. Parys, G. Bultynck, Bcl-2 proteins and calcium signaling: complexity beneath the surface, Oncogene 35 (2016) 5079–5092, https://doi.org/10.1038/onc.2016.31.
[8] D. Rojas-Rivera, C. Hetz, TMBIM protein family: ancestral regulators of cell death, Oncogene 34 (2015), https://doi.org/10.1038/onc.2014.6.
[9] C. Hidalgo, P. Donoso, M.A. Carrasco, The ryanodine receptors Ca2+ release channels: cellular redox sensors? IUBMB Life 57 (2005) 315–322, https://doi.org/10.1080/15216540500092328.
[10] D.M. Booth, B. Enyedi, M. Geiszt, P. Várnai, G. Hajnóczky, Redox nanodomains are induced by and control calcium signaling at the ER-mitochondrial interface, Mol. Cell 63 (2016) 240–248, https://doi.org/10.1016/j.molcel.2016.05.040.