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Cell Death and Immune Response: the Role of Necroptosis and Pyroptosis in Inflammation

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Cell death is an essential cellular process during development, but also facilitates the removal of damaged or infected cells, and is required for the resolution of innate and adaptive immune responses.

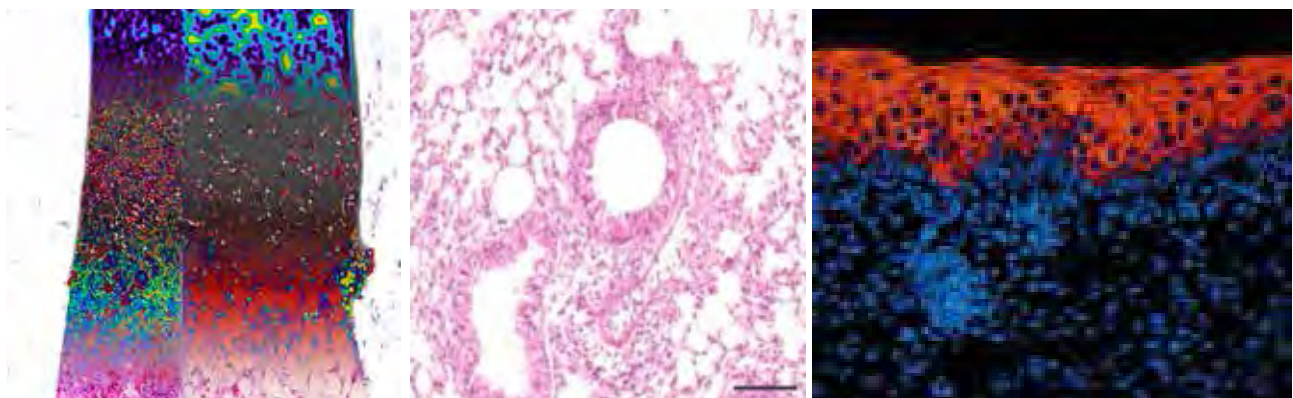
Our research focus is the understanding of the inflammatory response, with particular emphasis on novel NLRs (Nucleotide-binding domain and Leucine-rich repeat containing Receptors), and the non-apoptotic forms of cell death during infection. In particular we are interested in how pathogens (viruses and bacteria) are recognized by the innate immune system to facilitate these signals and how some pathogens evolve to target these mechanisms and prevent the host inflammatory response.

Recently, we discovered a physiological role for NLRP1 in driving a lethal, systemic inflammatory disease that is triggered by Caspase-1 activation and IL-1 β production. Remarkably, active NLRP1 triggered a Caspase-1-dependent form of cell death, known as pyroptosis. This cell death affected

hematopoietic stem and progenitor cells (HSPC), resulting in leukopenia at steady state, and cytopenia, bone marrow hypoplasia and immunosuppression, during periods of hematopoietic stress induced by chemotherapy or viral infection. Our recent research into how pathogens modulate complexes such as the NLRP1 inflammasome has defined mechanism by which *Vaccinia Virus* protein, F1L, target inflammasomes directly by binding and inhibiting the NLRP1 inflammasome formation. These findings reveal novel mechanism for viruses to evade host innate immune responses. Furthermore, we recently changed the thinking of necroptosis, which was thought to be RIPK1-dependent. We found the opposite, namely, that RIPK1 acts as a negative regulator of necroptosis, and loss of RIPK1 results in a lethal multi-organ systemic inflammatory response.

Publications

O'Donnell JA, Kennedy CL, Pellegrini M, Nowell CJ, Cengia L, Masters SL, Hartland EL, Roberts AW, **Gerlic M**, Croker BA. Fas controls neutrophil lifespan during viral and bacterial infection. *J Leukoc Biol*, December 3, 2014, doi: 10.1189/jlb.3AB1113-594RR.



Non-apoptotic induce inflammation. Inflammasome dependent lung inflammation during *vaccinia virus* infection (Left panel); Pyroptotic dependent bone marrow failure after chemotherapy treatment (Middle panel); Necroptotic dependent skin inflammation (Right panel).

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Reviews

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