Title: Molecular mechanisms of innate immunity and inflammatory cell death

Abstract: The innate immune system is the critical first line of defense against invading pathogens and cellular insults, and mutations in innate immune genes are associated with diseases. Pattern recognition receptors sense pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) and induce an immune response characterized by inflammation and cell death. Among the most well-characterized programmed cell death (PCD) pathways are pyroptosis, apoptosis, and necroptosis. While these pathways have historically been defined as segregated and independent processes, in-depth characterization shows significant crosstalk among them. Decades of observations and compelling genetic evidence suggest there is a unique inflammatory PCD pathway called PANoptosis, which integrates components from other cell death pathways and is regulated by multifaceted PANoptosome complexes; the totality of biological effects observed in PANoptosis cannot be accounted for by any of the other PCD pathways alone. The molecules ZBP1, caspase-8, RIPK1, and AIM2 have been identified as upstream sensors and important PANoptotic molecules. PANoptosis can be induced by a variety of infections, PAMPs, and DAMPs. For example, synergistic activity of TNF and IFN-γ during disease, including COVID-19, causes severe outcomes via PANoptosis, inducing further cytokine release, tissue damage, and death; these findings establish a distinct mechanistic basis of cytokine storm. Additionally, ZBP1-mediated PANoptosis plays a critical role in several infections. Furthermore, therapeutically targeting PANoptosis can improve disease outcomes. Neutralizing TNF-α and IFN-γ reduces SARS-CoV-2–induced mortality in mice. Conversely, activating PANoptosis through treatment with IFN and the nuclear export inhibitor KPT-330 drastically regresses tumors in a mouse model. Overall, the conceptual advancement and framework established through PANoptosis allow us to further investigate the significance of innate immune-mediated cell death in various physiological and pathological settings. Improved understanding of innate immune-mediated cell death, PANoptosis, is critical to inform the next generation of treatment strategies for cancers, infectious diseases, and conditions associated with a hyperactive innate immune response, cytokine release, and severe inflammation.