Modulation of cytokine storm and tumorigenesis by innate immunity

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Abstract

Cell death has been associated with pathologies observed in cytokine storm syndromes caused by excessive production of pro-inflammatory cytokines and interferons during SARS-CoV-2 infection. Of the multiple inflammatory cytokines or interferons produced by innate immune cells during the viral infection, combination of TNF and IFN-γ specifically induced cell death, which is characterized by gasdermin–mediated pyroptosis, caspase-8–mediated apoptosis, and MLKL–mediated necroptosis, collectively called PANoptosis. Mechanistically, the STAT1/IRF1 axis activated by TNF and IFN-γ co-treatment induced nitric oxide production to drive PANoptosis. Neutralizing TNF and IFN-γ protected mice from lethality in various models of cytokine storm syndromes. Since resisting cell death is one of the hallmarks of tumorigenesis, innate immunity and cell death can be exploited to treat cancer. TNF and IFN-γ induced PANoptosis in several human cancer cell lines and inhibited the tumor development in tumor transplant model. Moreover, IRF1 deficiency led to colorectal tumorigenesis. In addition to TNF and IFN-γ, PANoptosis was induced by KPT-330, a FDA approved drug for the treatment of refractory multiple myeloma, in the presence of IFNs. The IFN inducible, ADAR1 suppressed KPT and IFN–induced PANoptosis by interacting with ZBP1. Treating mice with KPT and IFN regressed melanoma in a ZBP1-dependent manner. Altogether, innate immunity and cell death can be harnessed to treat cytokine storm associated diseases and tumorigenesis.