STING agonist-induced cytokine production with anti-HBV activity is accompanied by immunogenic cell death of monocytes

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Abstract

The cyclic-GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway recognizes cytosolic double-stranded DNA (dsDNA), a sign of viral infection or cell damage. Activation of the pathway stimulates immune cells to secrete type I interferons (IFNs) and various proinflammatory cytokines. These immunomodulatory proteins further induce multiple regulatory immune processes with antiviral or antitumoral properties.

As the cGAS-STING pathway can also by activated by STING agonists, we investigated their anti-HBV properties. We demonstrated that STING agonists induced secretion of a broad portfolio of cytokines by peripheral blood mononuclear cells (PBMCs). Moreover, the PBMC-derived cytokines reduced HBV antigen and DNA secretion, and viral RNA in infected primary human hepatocytes by up to 90%. However, the anti-HBV cytokine production activated by STING agonists also caused a dramatic monocyte depletion within the PBMCs.

To better understand the mechanisms of the STING agonist-induced monocyte loss, we analyzed multiple cell death pathways. We particularly focused on an immunogenic regulated cell death called PANoptosis, which combines characteristics of apoptosis, pyroptosis and/or necroptosis. Upon STING agonist treatment, we detected active caspases 3 and 7, and active caspase 1 demonstrating involvement of apoptosis, and pyroptosis, respectively. Furthermore, STING agonist-treated PBMCs also secreted interleukin 1β (IL1β) and IL18, which are processed by the pyroptotic inflammasome. Finally, based on the analysis of pseudokinase MLKL phosphorylation, we suggest that necroptosis may also be induced.

Overall, STING agonist-induced monocyte depletion could be mediated by PANoptosis. As PANoptosis is immunogenic in nature, the monocyte death may not be an unwanted side effect of STING agonist treatment. Rather, it could be an immunoregulatory mechanism inhibiting the primary cytokine secretion to prevent dangers of cytokine storm, and to allow activation of secondary immune processes. Therefore, understanding the mechanisms of STING agonist-dependent monocyte cell death could broaden the investigation of the STING agonist therapeutic potential.