STING agonists induce monocyte depletion with characteristics of multiple regulated cell deaths

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Abstract

Double-stranded DNA and cyclic dinucleotides activate the cyclic-GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway, which leads to the production of type I interferons (IFNs) and proinflammatory cytokines by immune cells. These compounds further mediate numerous regulatory immune processes with antiviral or antitumoral properties. Therefore, activators of the cGAS-STING pathway are being investigated for their therapeutic potential.
To better understand the immune orchestration induced by STING agonists, we investigated their effect on peripheral blood mononuclear cells (PBMCs), a physiologically relevant complex of immune populations. We demonstrated that STING agonists induce the secretion of a broad portfolio of proinflammatory cytokines. However, treatment with STING agonist is also associated with robust monocyte depletion.
We focused on the mechanisms involved in STING agonist-induced monocyte depletion, aiming on cell death, particularly PANoptosis. This regulated cell death combines characteristics of apoptosis, pyroptosis, and/or necroptosis, and is immunogenic. We first demonstrated the involvement of apoptosis by detecting active caspases 3 and 7. Second, we showed the induction of pyroptosis by detecting active caspase 1 and the secretion of interleukin 1β (IL1β) and IL18, which require processing by a pyroptotic machinery. Third, analysis of the phosphorylation of the pseudokinase MLKL suggests that necroptosis may also be activated. Therefore, taken together, PANoptosis could represent a mechanisms of monocyte cell death induced by STING agonists.
Overall, monocyte death induced by activation of the cGAS-STING pathway via PANoptosis could serve as an immunoregulatory mechanism inhibiting cytokine secretion to prevent, for example, overstimulation or dangers of cytokine storm. On the contrary, the immunogenic character of monocyte death could be important for secondary immune processes activation. Unraveling these mechanisms could therefore expand the understanding of the therapeutic potential of STING agonists.