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L-18
STING AGONISTS ACTIVATE MULTIPLE REGULATED CELL DEATH MECHANISMS IN MONOCYTES

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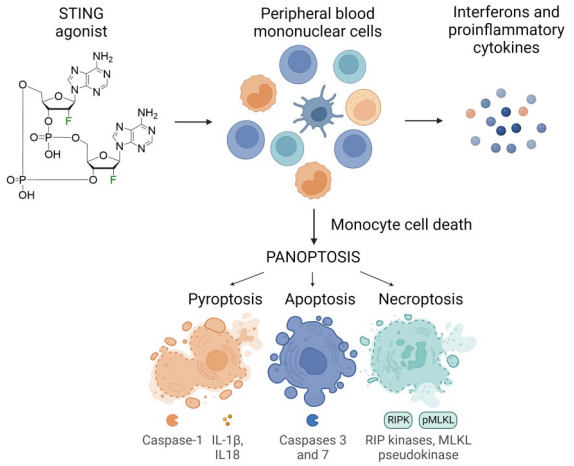
Stimulation of the innate immune responses using agonist of pattern recognition receptors is one of the investigated therapeutic approaches for treatment of chronic diseases, such as cancer or chronic infections. The cyclic-GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway is one potential targetable pathway, as it naturally recognizes double-stranded DNA in the cytoplasm, and in turn triggers secretion of interferons and other proinflammatory cytokines[1]. The secreted cytokines further mediate various innate immune processes, some of which also induce adaptive immune responses against viral infection or tumors[1,2]. Importantly, the cGAS-STING pathway can be activated also by small molecules, STING agonists[2,3].

However, the cGAS-STING pathway activation can also lead to cell death via multiple regulated cell death pathways[4]. Indeed, we discovered, that STING agonists induced cell death of monocytes within the population of peripheral blood mononuclear cells[3]. The phenotype of dying cells had apoptotic characteristics but we could not fully exclude the involvment of other regulated cell death pathways.

Therefore, we further investigate the mechanisms of STING agonist-indcued cell death of monocytes. We focus on the phenomenon called PANoptosis, a regulated cell death combining features of pyroptosis, apoptosis and/or necroptosis[5]. So far, we detected activated caspases 3 and 7, which characterize active apoptosis. We also demonstrated involvement of pyroptosis by showing activation of caspase 1 as well as secretion of interleukin 1β (IL1β) and IL18, which require processing by inflammasome. Eventhough the activation of necroptosis is yet to be determined, we claim that the STING agonist-induced cell death of monocytes involves at least two pathways (apoptosis and pyroptosis).

As monocytes are supposedly the main producers of proinflammatory cytokines induced by the STING agonists, rapid negative feedback may be needed to tightly regulate the accute inflammation in organism to prevent the potential life-threatening cytokine storm. Moreover, acute inflammation inhibits the subsequent adaptive immune processes. As such, the monocyte cell death via apoptosis and pyropotosis (possibly PANoptosis) could be a natural immunoregulatory mechanism inhibiting the primary proiflammatory cytokine secretion while being immunogenic for further activation of adaptive immune responses.



Scheme 1. **In peripheral blood mononuclear cells (PBMCs), the STING agonists not only trigger secretion of a broad portfolio of proinflammatory cytokines, but they also induce monocyte cell death with characteristics of multiple regulated cell death pathways.** (Created with BioRender.com)

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