STING AGONISTS INDUCE ROBUST CYTOKINE SECRETION AND RAPID MONOCYTE CELL DEATH IN PERIPHERAL BLOOD MONONUCLEAR CELLS

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The cyclic-GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway plays a central role in recognition of the double-stranded DNA in cytoplasm, a sign of cell damage or infection. Upon activation, the pathway triggers production of interferons and proinflammatory cytokines by immune cells. These immune mediators further modulate regulatory immune processes with antitumoral and antiviral properties. Therefore, activators of the cGAS-STING pathway are being investigated for their therapeutic potential.

We have previously demonstrated that STING agonists induce secretion of a broad portfolio of proinflammatory cytokines in peripheral blood mononuclear cells (PBMCs) *in vitro*. However, the treatment with STING agonists also triggers a robust monocyte depletion.

To better understand the immune orchestration induced by STING agonists, we further investigated the mechanisms of the STING agonist-induced monocyte depletion. We particularly focused on PANoptosis, a regulated cell death combining characteristics of apoptosis, pyroptosis, and/or necroptosis. Therefore, we investigated the activation of effector apoptotic caspases 3 and 7, pyroptotic caspase 1, and phosphorylation of necroptotic pseudokinase MLKL. We showed that both apoptotic and pyroptotic caspases were activated in monocytes upon STING agonist treatment. Yet, we are still to prove whether the necroptotic mechanisms are also induced. Moreover, we aim at addressing metabolic phenotypes underlying STING signalling in monocytes.

Taken together, STING agonist treatment induces at least two different regulated cell death pathways – apoptosis and pyroptosis, suggesting that PANoptosis could be involved in the monocyte cell death. The STING agonist-induced monocyte cell death could act an immunoregulatory mechanism inhibiting cytokine secretion to prevent e.g. overstimulation or dangers of cytokine storm. On the contrary, the immunogenic character pyroptosis (or PANoptosis) of monocyte death could mediate the activation of secondary immune processes. Unravelling these mechanisms along with metabolic phenotypes could therefore expand the understanding of the therapeutic potential of STING agonists.