MONOCYTE CELL DEATH INDUCED BY STING AGONISTS COMBINES APOPTOSIS, PYROPTOSIS AND CASPASE 8 ACTIVATION

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The cyclic GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway recognizes double-stranded DNA in cytoplasm. Activation of the pathway induces secretion of proinflammatory cytokines and subsequently regulates immune mechanisms.[1] The pathway can also be triggered by small molecule-based STING agonists.[2] As such, the cGAS-STING pathway is of therapeutic interest in the field of viral infections and cancer.[1,2] Importantly, activation of the cGAS-STING pathway can also lead to cell death regulated.[3] We previously demonstarted that STING agonists induce apoptosis in human monocytes;[2] however, the precise processes involved are still under investigation.

Therefore, we further analyzed the mechanisms underlying STING agonist-induced cell death in monocytes. We observed the activation of apoptotic caspases 3 and 7, and pyroptotic caspase 1, gasdermin D, and the secretion of interleukin 1β (IL1β) and IL18. However, we did not detect activation of the necroptotic RIP kinases and the pseudokinase MLKL. Interestingly, we observed active caspase 8, regulates not only apoptosis but also pyroptosis and necropotosis.[4] Furthermore, we detected a cleaved fragment of RIPK1 consistent with caspase 8-mediated cleavage, suggesting that caspase 8 may negatively regulate the necroptotic pathway. Additionally, STING agonists induced mitochondrial dysfunction, indicating a potential role for mitochondria in the regulation of cell death.

Taken together, our findings provide new insights into the effects of the cGAS-STING pathway in immune cells, highlighting its potential in therapeutic applications.

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