STING AGONIST-INDUCED CD14+ MONOCYTE DEPLETION INVOLVES MULTIPLE REGULATED CELL DEATH MECHANISMS

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The immune cells respond to the double-stranded DNA (dsDNA) or cyclic dinucleotide (CDN)-mediated stimulation of the cyclic-GMP-AMP synthase – stimulator of interferon genes (cGAS-STING) pathway by secretion of type I interferons (IFNs) and proinflammatory cytokines[1,2]. The cytokines and IFNs mediate multiple innate immune processes further bridging to adaptive immune responses, among which the antiviral defence and immune surveillance are at the forefront of research interest[1,2].

Apart from the expected cytokine secretion, STING agonists also caused a complete depletion of CD14+ monocytes in peripheral blood mononuclear cells (PBMCs). Moreover, both CD14+ monocyte depletion and type I IFN secretion was blocked by the cGAS-STING pathway inhibition[3].

We have previously identified that apoptosis was involved in STING agonist-induced CD14+ monocyte depletion[3]. Hence, we further investigate the cell death mechanisms induced by the cGAS-STING pathway activation focusing on the combination of pyroptosis, apoptosis and necroptosis, so called PANoptosis[5]. First, we elaborated on the involvement of apoptosis[3] by analyzing the activation of caspases 3 and 7. Second, we demonstrated that STING agonists induce secretion of interleukin 1β (IL1β) and IL18, both cytokines that require processing by the inflammasome - a marker of pyroptosis[4]. Third, despite detected increased levels of active pyroptotic caspase 1, the involvement of necroptosis remains to be clarified. Nevertheless, based on our preliminary results, we deduce that at least two regulated cell death pathways (apoptosis and pyroptosis) are involved in the STING agonist-dependent CD14+ monocyte depletion. The cGAS-STING pathway activation-induced death of CD14+ monocytes could present an immunoregulatory mechanism, which inhibits the primary robust cytokine secretion, thus preventing potential dangers of prolonged inflammation. Moreover, as pyroptosis is of immunogenic character[4], such CD14+ monocyte cell death could further mediate activation of secondary immune processes including the adaptive immune mechanisms.

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