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The role of two NODs (nucleotide-binding oligomerization domain) and a STING (stimulator of interferon gene) in the tale of DMXAA

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DMXAA (5,6-dimethylxanthenone-4-acetic acid), developed at the ACSRC, entered human clinical trials based on its excellent curative activity against a range of preclinical tumours in mice. Phase 2 clinical trials were promising, but phase 3 trials in combination with chemotherapy failed to show survival benefit against lung cancer compared to chemotherapy alone. The reason for DMXAA’s failure in phase 3 has been hotly debated. As part of our efforts to elucidate the basis of its interspecies differences, we showed that DMXAA has a diminished capacity to stimulate cytokine production in cultured human leucocytes compared to that in murine leucocytes. Moreover, we identified XAA analogues that showed superior activity to DMXAA in stimulating IL-8, IL-6 and TNF-α production by human leucocytes. These ‘human-selective’ analogues did not stimulate cytokine production in mouse cells however.

The molecular mechanisms underlying DMXAA’s cytokine-inducing/immune-modulatory activity, a key component of DMXAA’s durable antitumour activity in mice, has yet to be fully elucidated. The NF-κB pathway, the stimulator of interferon genes (STING) and TBK1-IRF-3 signaling axis, the NOD signaling pathways, and at least 3 members of the MAPK superfamily and redox signaling have all been implicated. Recent studies showed that activation of STING in murine macrophages appears essential for DMXAA-induced IFN-β production. Despite 89% structural similarity in the two homologues, DMXAA binds murine STING but not human STING, and DMXAA does not stimulate IFN-β production in human monocytic/macrophage cell lines.

Preliminary studies suggest that the human-selective XAA analogues do not bind to either murine or human STING, and nor do they induce IFN-β in murine or human monocytic/macrophage lines in culture. IL-8 is the most abundantly produced cytokine in human peripheral blood leucocyte cultures, and the production of this cytokine is not dependent on STING activation. The NOD homologues may exhibit less species-specificity, as DMXAA has been shown to activate human NOD 2. Studies are underway to determine if the human-active XAA analogues stimulate IL-8 production through NOD-dependent pathways.