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Heme Activates the Inflammatory Caspases to Induce Cytokine Release and Cell Death

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Abstract: Background: Increased levels of extracellular heme from red blood cell destruction underlie the pathophysiology of several disease states, including bacterial sepsis, malaria, and sickle cell disease (SCD). A consequence of this excessive extracellular heme is uncontrolled-inflammation. Heme has been shown to activate caspase-1, an enzyme required to ensure correct regulation of inflammatory signaling. Caspase-1 is recruited to inflammasomes in response to pathogenic and non-pathogenic insults, and stimulates maturation of the pro-inflammatory cytokines, interleukin (IL)-1β and IL-18. The other inflammatory caspases, -4 and -5 (and their murine homolog caspase-11) also promote IL-1β release by inducing an inflammatory form of cell death called pyroptosis.

Hypothesis: We hypothesize that heme activates caspase-4 and caspase-5 to differentially regulate caspase-1 activation, cytokine release and cell death, promoting inflammatory complications in hemolytic conditions such as Sickle Cell Disease (SCD).

Results: We show in primary human macrophages that heme induced IL-1β release, and this was increased in cells derived from patients with SCD. Heme also promoted the oligomerization of the inflammatory caspases, caspase-1, -4 and -5 in macrophages, a step required for their activation. While caspase-1 activation was inflammasome-dependent, silencing of inflammasome proteins did not prevent heme-induced activation of caspase-4 or -5. This indicates that caspase-4 and -5 are activated independent of inflammasomes. Loss of caspase-4 or -5 blocked heme-induced IL-1β release, suggesting a co-operative regulation between these two caspases and caspase-1, rather than a redundant function. Interestingly, cells lacking caspase-4 showed a reduction in heme-induced cell-death.

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Conclusion : Altogether, our results provide evidence that both caspase-4 and caspase-5 are essential for heme-induced IL-1β release, while caspase-4 is the primary contributor to heme-induced cell death. In addition, we identified that extracellular heme acts as a damage associated molecular pattern (DAMP) that can promote canonical and non-canonical inflammasome activation as a key mediator of sterile inflammation in macrophages.

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