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Therapeutic strategies in inflammasome mediated diseases of the liver

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Summary

Tissue stress and cell death result in inflammation even in the absence of pathogens. Such sterile inflammation is dependent on a cytosolic complex of proteins inside immune cells termed the inflammasome. This complex converts two groups of extracellular signals into an inflammatory response via activation of caspase-1 and secretion of IL-1β and IL-18. Group 1 signals are typically TOLL like receptor agonists and result in transcriptional upregulation of inflammasome components and pro-cytokines. Group 2 signals are diverse, ranging from uric acid to ATP, and lead to assembly and activation of the inflammasome complex. Inflammasome components are required for a wide range of acute and chronic pathologies, including experimental alcoholic and non-alcoholic steatohepatitis, and drug-induced liver injury. Collectively, group 1 and 2 signals, inflammasome components, and cytokine receptors provide a rich source of therapeutic targets. Many of the advances in the field have come from standard reductionist experiments. Progress in the understanding of complex human systems will, however, be dependent on novel strategies such as systems analysis, which analyze large data sets to provide new insights.
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Introduction

The development of inflammation after tissue injury has been known since ancient times, and occurs in the absence of pathogens. Such sterile inflammation (SI) is pervasive in a wide range of pathologies, and is significant because it can increase the overall organ damage after the primary insult. Alcoholic and non-alcoholic steatohepatitis (ASH and NASH), and drug induced liver injury (DILI) have SI as an important component of liver damage. Such a generic recognition of a role for SI, and characterization of some of the cellular and cytokine components was complemented by a number of interconnecting developments. Firstly was the theoretical proposal that cell death results in the release and production of molecules which are not present in the extracellular environment during health (damage associated molecular patterns – DAMPs). The second was the identification of a range of DAMPs which possess a wide range of structures from true pattern molecules such a nuclear and mitochondrial DNA, to small molecules like ATP and large crystals like uric acid. The third was identification of the cell surface receptors and mechanisms activated by DAMPs, and the fourth was identification of the cytosolic machinery in innate immune cells which is activated by DAMP signals and has been termed the inflammasome. These discoveries overlapped with much of what was known about immune activation by pathogens, by pathogen associated molecular patterns (PAMPs), including the fact that many of the PAMP receptors such as TLRs are also activated by DAMPs.

Key Points

- Cell death results in inflammation even in the absence of pathogens (sterile inflammation)
- Sterile inflammation can increase organ damage
- The inflammasome is a cytosolic protein complex that is required for the development of sterile inflammation
- Many liver diseases such as alcoholic steatohepatitis, non-alcoholic steatohepatitis, and drug-induced liver injury have sterile inflammation as a major component
- The above pathways have allowed for the development of novel therapies and the repositioning of older therapies

The current understanding of activation of inflammasome pathways in SI is shown in Fig. 1. Two broad types of signals are required in most cells for full activation of this pathway and production of the inflammatory cytokines IL-1β and IL-18. Signal 1 is delivered by a number of TLR ligands (Table 1) and results in transcriptional upregulation of pro-IL-1β pro-IL-18 and inflammasome components. A number of cytokine receptors share the signaling domain MyD88 used by most TLRs and can

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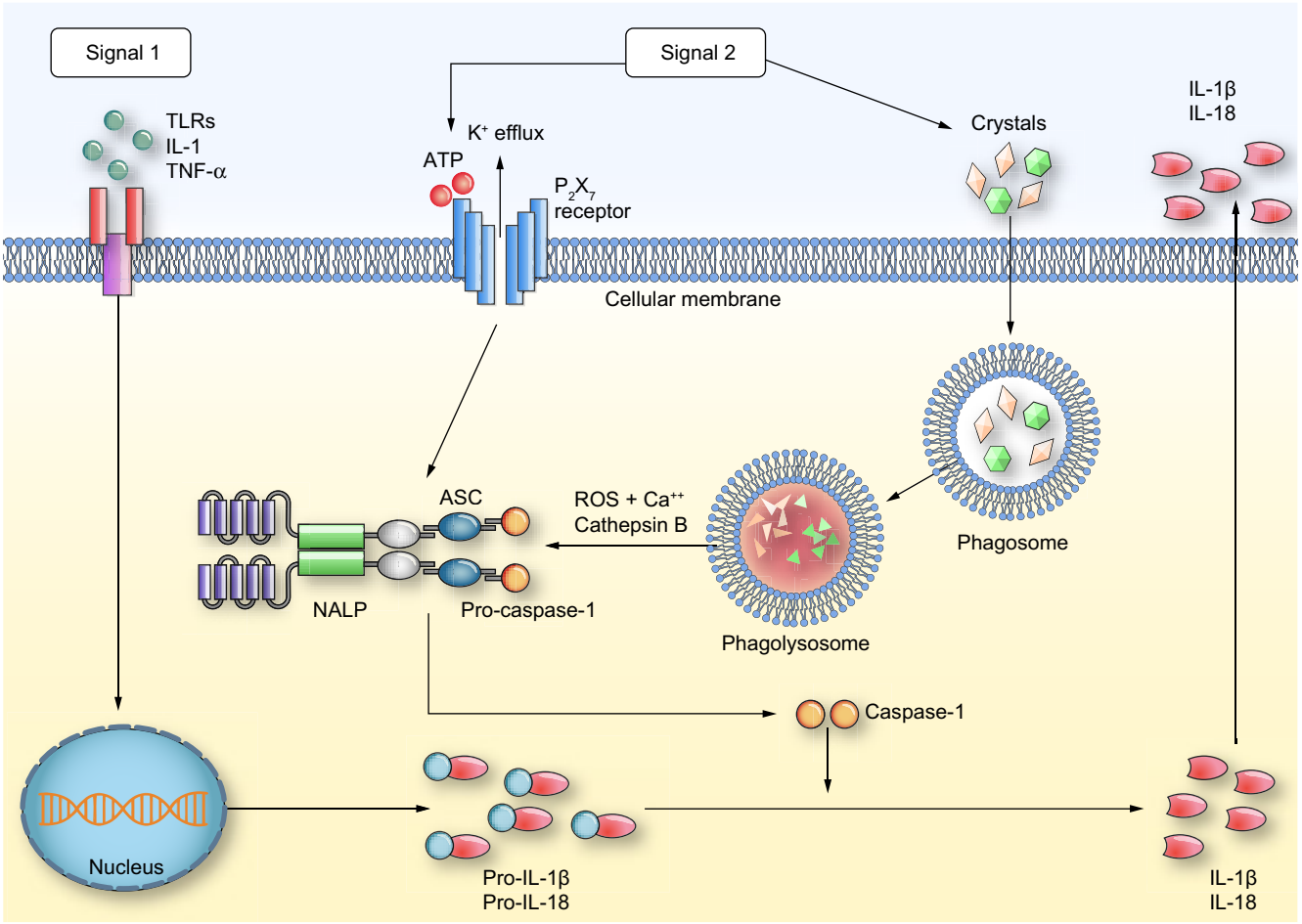

Fig. 1. Mechanisms of inflammasome activation. Two types of signals are required for inflammasome activation and production of mature IL-1β and IL-18. *Signal-1:* This results in the production of pro-IL-1β and pro-IL-18 through interaction of various DAMPs/PAMPs and cytokines like TNF-α with TLRs and TNFR. *Signal-2:* This leads to inflammasome activation through multiple signaling pathways. MSU and other crystals result in the formation of phagolysosomes. Another pathway of inflammasome activation is via activation of the P2X7 receptor. The activation of inflammasome results in the cleavage and activation of the proteases caspase-1 which subsequently cleaves pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18 that are secreted out of the cell. ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; DAMPs, disease associated molecular patterns; IL-1β, interleukin-1beta; IL-18, interleukin-18; MSU, monosodium urate; PAMPs, pathogen associated molecular patterns; ROS, reactive oxygen species; TLRs, toll like receptors; TNF-α, tumor necrosis factor-alpha; TNFR, tumor necrosis factor receptor.

provide signal 1 allowing the possibility of a positive feedback loop. Signal two can be provided by a highly diverse range of molecules (Table 1) and result in assembly of the inflammasome machinery, which includes cytosolic proteins ASC (apoptosis-associated speck-like protein containing a CARD), NALP (NACHT, LRR, and PYD-containing protein) and caspase-1. Mitochondria likely form a central component proximal to inflammasome activation and integrate these diverse signals. The key step in inflammasome activation is cleavage and activation of caspase-1 which can subsequently cleave and activate the pro-cytokines pro-IL-1β and pro-IL-18. Both these cytokines are relatively proximal in the inflammatory cascade and result in the production of TNF-α and IFN-γ which can induce liver injury by a variety of mechanism.

The inflammasome and liver disease

The typical first line of investigation is to test experimental models of liver disease in mice genetically deficient (knockout, KO) in individual inflammasome components. This has been done for several, but not all, inflammasome components in experimental models of ASH, NASH, ischemia reperfusion (IR) and DILI. Such approaches have limitations but there is a broad consensus that many steps of the inflammasome pathways shown in Fig. 1 are necessary for the development of experimental ASH, NASH, IR and DILI (Table 1).

TLR4 and 9 are the ones most reported, and this may simply be because they are the most investigated.

Cell specific roles of inflammasome components

The functional roles of inflammasome components were initially identified in innate immune cells particularly macrophages and explain their rapid production of inflammatory mediators in response to pathogen and damage associated molecular patterns. In the liver, this suggests a major role for inflammasome pathways in Kupffer cells (KC), and this has been confirmed in a