Presentation:
Signaling PAMPs and DAMPSs - Role of TLRs, NLRs and RLRs

Speaker:
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Abstract:
Our understanding of innate immunity has been dramatically improved following the identification of three families of pathogen sensors: Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs). TLRs recognize microbial structures (from Gram-positive and Gram-negative bacteria, mycobacteria, RNA and DNA viruses, fungi and protozoans) in the earliest phase of the host defence response, and induce the expression of many immune and inflammatory genes, the products of which are tailored to drive the immune mechanisms necessary for eliminating the invading pathogen. To date, NLRs have only been shown to detect bacteria, whereas RLRs only recognize viruses. Some NLRs, in particular, NOD1 and NOD2, activate nuclear factor (NF)-κB, a key transcription factor for inflammatory and immune gene expression. Furthermore, the NLRs NALP1, NALP3 and Ipaf activate caspase-1, a key inflammatory caspase that processes the pro-forms of interleukin (IL)-1β and IL-18, two crucial pro-inflammatory cytokines. The RLRs (RIG-I, MDA-5 and lgp-2), similar to anti-viral TLRs (TLR3, TLR7, TLR8 and TLR9), detect viral nucleic acids and activate certain interferon-regulated factor (IRF) family members. While MDA-5 detects long double-stranded RNA, 5´triphosphate RNA, now termed 3pRNA is the specific ligand of RIG-I. NLRs and RLRs can trigger a subset of responses similarly to TLRs, and act co-ordinately in these circumstances. Important interactions occur between TLRs and certain NLRs for inducing the pro-inflammatory cytokine interleukin (IL)-1β. TLRs induce pro-IL-1β production and prime NLR-containing multi-protein complexes, termed 'inflammasomes' to respond to their cognate ligands. Furthermore, a connection of RLRs and NLR-containing inflammasomes has been proposed. These recent discoveries return IL-1β to the forefront for host defence and inflammation, with the recent advances providing a molecular explanation for phenomena first described twenty years ago. Intriguingly TLRs, NLRs and RLRs are not only sensors of pathogens but also detect endogenous damage-associated molecular pattern molecules (DAMPs) released during cell death. Moreover, effector cells of innate and adaptive immunity upon activation by pathogen-associated molecular patterns (PAMPs) can secrete DAMPs such as high mobility group box 1 (HMGB1) via nonclassical pathways. Endogenous DAMPs and exogenous PAMPs therefore can convey a similar message and elicit similar responses. This information will lead to novel strategies for effective biologic therapy of infection, of inflammatory disease and of cancer.