The inflammasome

Inflammasomes are multi-protein specialized signaling platforms critical for the **regulation of innate immune and inflammatory responses** (**Choi AJ, et al,Mol Cells 2014**). They are **composed of** a NOD-like receptor (NLR)/an AIM-like receptor (ALR), the adapter molecule apoptosis-associated speck-like protein that contains a caspase recruitment domains or CARD (ASC), and caspase-1 (**Mankan AK, et al, Clinical and Experimental Immunology 2012)**.

Mechanism of action

In response to several stimuli, like infectious microbes and molecules derived from host proteins, **caspase-1** is activated. This leads to processing and secretion of **pro-inflammatory cytokines** such as interleukin (IL)-1β and IL-18 and cause a rapid and pro-inflammatory form of cell death called **pyroptosis** (**invivogen.com**).

The most intensely studied inflammasome is the **NLRP3 inflammasome (Chen G, et al, Sensors 2010).** It is activated by a broad variety of stimuli, including danger signals, crystalline substances and microbial toxins.

Both **signal 1 and signal 2** are required for NLRP3 inflammasome activation: signal 1, also known as the priming signal, is mediated by microbial ligands recognized by TLRs or cytokines such as TNF-α. Signal 1 activates the NF-κB pathway, leading to upregulation of pro-IL-1β and NLRP3 protein levels. The signal 2 is mediated by numerous PAMP or DAMP stimulation, and promotes the assembly of ASC and pro-caspase-1, leading to activation of the NLRP3 inflammasome complex (**Choi AJ, et al,Mol Cells 2014**).

Inflammasome and diseases

Inflammasome activation is crucial for host defense to pathogens but recent studies have also found a role for the inflammasomes in the pathogenesis of several **inflammatory diseases** such as inflammatory bowel disease, rheumatoid arthritis and atherosclerosis

Additionally, increasing evidence in mouse models, supported by human data, strongly implicates an involvement of the inflammasome in the initiation or **progression of diseases with a high impact on public health**, such as metabolic disorders and neurodegenerative diseases.

In **atherosclerosis**, free fatty acids (**FFA**) can **prime the NLRP3** inflammasome through TLR2-TLR4 signaling. The NLRP3 inflammasome is activated through cathepsin release. Phagocytosis of extracellular cholesterol crystals may also contribute to inflammasome activation. **Cathepsin inhibition** prevents the NLRP3 inflammasome activation induced by cholesterol crystals.

In **Alzheimer's disease**, CD36 mediates the internalization of soluble amyloid-β and its intracellular conversion to fibrillary amyloid-β. This leads to **disruption of the phagolysosome** and activation of the NLRP3 inflammasome due to cathepsin B release. **Cathepsin B inhibition** prevents amyloid-β–induced NLRP3 activation (**Guo H, et al, Nature medicine 2015).**

Therapy

The chronic **deposition of Aβ (amyloid-β peptide)** stimulates the persistent activation of **microglial cells** in Alzheimer´s disease (AD). Increased IL-1β (interleukin 1β) levels have been implicated in the response to Aβ deposition. IL-1β is produced as a biologically inactive pro-form and requires caspase-1 for activation and secretion. Caspase-1 activity is controlled by inflammasomes. So **there is a relation between Alzheimer's disease and inflammasomes.**

In fact, activation of the NLRP3 inflammasome, induced by amyloid-β peptide, enhances Alzheimer progression by mediating a harmful chronic inflammatory tissue response.

Scientists made a **experiment to study this relation**, using mice carrying genes associated with familiar Alzheimer disease. They discovered that **if genes for NLRP3 or caspase-1 were inhibited, mice were protected** from loss of spatial memory and other problems associated to Alzheimer Disease. These results reveal an **important role for the NLRP3** / caspase-1 axis in Alzheimer pathogenesis, and suggest that NLRP3 inflammasome inhibition **represents a novel therapeutic intervention for Alzheimer (Heneka M, et al, Nature 2013).**