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Introduction

Innate immunity and adaptive immunity

The immune system consists of two major components: innate immunity, which provides early, general reactions to infections, and adaptive immunity, which later recognizes and reacts to microbial and non-microbial substances in specific manner.

Innate immunity … (cell types, process, etc.)

Adaptive immunity … (cell types, process, memory, etc.)

Cooperation between innate and adaptive immunity …

Endosomal and cytosolic PPRs

General model for innate immune response (PPR – adapter – kinases – TFs – effectors)

Membrane bound receptors: TLRs and CLRs

Cytosolic receptors: RIG-I, inflammasome, NLRs, cGAS

Transcription factors and transcriptional inflammatory response

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IRF5 signaling and autoimmune disease

The interferon regulatory factor (IRF) family of transcription factors plays a pivotal role in the development of immune cells and induction of cytokines that are important in immune and inflammatory responses (Honda and Taniguchi 2006, Tamura, Yanai et al. 2008). The mammalian IRF family consists of nine members, IRF1-9 (Ikushima, Negishi et al. 2013). Among these, IRF3 and IRF7 have been extensively studied and shown to be important for the induction of type-I interferons (IFNs) and other cytokines in response to a variety of stimuli, such as virus infection. For example, infection with RNA viruses leads to the activation of RIG-I like receptors (RLRs), which in turn activate the mitochondrial adaptor protein MAVS(Yoneyama, Kikuchi et al. 2004, Kawai, Takahashi et al. 2005, Meylan, Curran et al. 2005, Seth, Sun et al. 2005, Xu, Wang et al. 2005). MAVS then activates the kinase TBK1, which phosphorylates IRF3 and IRF7, causing these transcription factors to homodimerize and enter the nucleus to turn on type-I IFNs. MAVS also activates the kinase IKKβ, which activates NF-κB to induce pro-inflammatory cytokines. Stimulation of some Toll-like receptors (TLRs), especially those localized on the endosomal membranes such as TLR3, 4, 7, 8 and 9, also leads to strong activation of IRF3 and IRF7 to induce type-I IFNs(Noppert, Fitzgerald et al. 2007, Ikushima, Negishi et al. 2013).

Compared to IRF3 and IRF7, much less is known about how IRF5 is activated. However, genetic studies have provided compelling evidence for an essential role of IRF5 in the production of inflammatory cytokines, such as TNF-α and IL-6, in response to TLR ligands such as lipopolysaccharides (LPS) (Takaoka, Yanai et al. 2005). IRF5 also functions together with IRF3 and IRF7 to mediate type-I interferon production in response to viral infections (Lazear, Lancaster et al. 2013). In addition, IRF5 plays important roles in M1 macrophage polarization (Krausgruber, Blazek et al. 2011) and IgG class switching in B cells(Lien, Fang et al. 2010). Polymorphisms in the IRF5 gene have been linked to human autoimmune diseases, including systemic lupus erythematosus (Graham, Kozyrev et al. 2006) and Sjogren’s syndrome (Miceli-Richard, Comets et al. 2007). Thus, IRF5 is critical for regulating immune and inflammatory responses in health and disease(Lazzari and Jefferies 2014).

Similar to IRF3 and IRF7, IRF5 contains a DNA binding domain (DBD), an IRF association domain (IAD) and a Serine-rich region (SRR) at the C-terminus(Barnes, Moore et al. 2001, Barnes, Kellum et al. 2002). The SRR is phosphorylated in response to TLR stimulation or virus infection. The crystal structure of a human IRF5 mutant, S430D, which was proposed to mimic IRF5 phosphorylation, showed that IRF5 formed a dimer (Chen, Lam et al. 2008). However, the physiological phosphorylation sites of IRF5 had not yet been identified or validated. The kinase that mediates IRF5 phosphorylation was also unknown.

Cytosolic DNA sensing pathway

Xxx

Regulation of cGAS activity

Xxx

Goal of current research

Ddd

IKK2 is the kinase that activate IRF5 transcriptional activity

Xxx

STING is the predominant receptor for cGAS

Results

Conclusions and discussion

Material and methods

Purification of cGAS inhibitor

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