Seminar on Innate Immunity

Date / Time:
Thursday
4 November 2010
11am – 12.30pm

Venue:
Clinical Research Centre (CRC)
Symposium Rooms 2 & 3
@ Level 1, Block MD11, CRC, 10 Medical Drive
Singapore 117597

Convener:
Professor Naoki Yamamoto

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“RNA Virus Infection Activates NFkB by TRIM23 Dependent Ubiquitin Conjugation To NEMO Through a K27-type Of Ubiquitin Linkage ”

Professor Kunitada Shimotohno
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Abstract
Viral components induce strong type I IFN responses through the activation of toll-like receptors (TLRs) and intracellular cytoplasmic receptors such as an RNA helicase RIG-I and/or MDA5. According to recent studies, the NF-κB essential modulator NEMO (also called IKKγ) is crucial for this virus-induced antiviral response. However, the precise roles of signal activation by NEMO adaptor have not been elucidated. Here, we show that virus-induced IRF3 and NF-κB activation depends on the K(lys)-27-linked polyubiquitination to NEMO by the novel ubiquitin E3 ligase TRIM23 (Triparite motif protein 23). Virus-induced IRF3 and NF-κB activation, as well as K27-linked NEMO polyubiquitination, were abrogated in TRIM23 knockdown cells, while TRIM23 knockdown had no effect on TNFα-mediated NF-κB activation. Furthermore, in NEMO-deficient mouse embryo fibroblast cells, interferon-stimulated response element (ISRE)-driven reporter activity was restored by ectopic expression of wild-type NEMO. From these results, we conclude that TRIM23-mediated ubiquitin conjugation to NEMO is essential for TLR3- and RIG-I/MDA5-mediated antiviral innate and inflammatory responses.

“Trypsinogen 5 is under the control of interferon regulatory factors”

Professor Toshifumi Matsuyama
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Abstract
Interferons (IFNs) render cells resistant to viral infection and regulate cell growth and differentiation. They elicit the pleiotropic biological effects mainly by regulating the expressions of many interferon-stimulated genes (ISGs) mainly via interferon regulatory factors (IRFs). We have analyzed the roles of IRFs in vivo using the knock-out mice, and found that IRF2-deficient (IRF2−/−) mice showed early death compared to normal mice after lymphocytic choriomeningitis virus (LCMV) infection, with severe inflammation in the pancreas. The lethal acute pancreatitis is also induced by intra-peritoneal poly(I:C) challenge. The pancreatitis was abolished by further knocking-out IFNα receptor1 (IFNαR1) gene, indicating the importance of type1 IFN signaling via IFNAR1 to develop the poly(I:C)-induced pancreatitis in IRF2−/− mice. To identify the molecules involved in the poly(I:C)-induced pancreatitis in IRF2−/− mice, we thoroughly examined the gene expression levels in the pancreas using Affymetrix DNA microarray system covering 35,000 gene probes, before and after 250 μg poly(I:C) injection to IRF2−/− mice and wild-type mice. Fourteen annotated genes were up-regulated more than 10-fold in IRF2−/− mouse, and nine genes were down-regulated more than 10-fold, compare to the wild-type mouse. The up-regulation of trypsinogen 5, but not other trypsinogen family members 1 and 2, by inactivating IRF2 gene was noteworthy and it reached about thousand-fold. From enzymatic analysis, trypsinogen5 was resistant to Spink3, a major endogenous trypsin inhibitor in the pancreas, compared to the two major pancreatic trypsinogen genes. Furthermore, trypsinogen 5 is directly regulated by IRF family members. Possible role of IFN-stimulated genes in the pancreatitis model will be discussed.