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Analysis of the IRF-3- or HMGB1-mediated regulation of innate immune responses against nucleic acid

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Abstract

Pattern recognition receptors (PRRs) activate immune responses against microbial infection through detecting pathogen-specific molecules (pathogen-associated molecular pattern; PAMPs) such as viral/bacterial nucleic acids, cell wall, and flagellin. Among them, nucleic acids are known to be a potent immune activator, which is thought to relate pathological conditions of infectious diseases, autoinflammation and autoimmunity. So far, two types of PRRs have been identified; membrane-bound Toll-like recepoters (TLRs) and cytosolic RIG-I-like receptors (RLRs). Both of the receptors, when they recognize their cognitive nucleic acids, induce potent immune responses through the activation of their own signaling pathways. However, the sensing mechanisms of nucleic acids and its signaling are not fully discovered. Recently, we have found that RLR-activated interferon regulatory factor (IRF)-3 bound to promoter region of the interleukin (IL)-12p40 gene and suppressed the induction of IL-12p40 mRNA driven by TLR-activated IRF-5 in a way of their competitive binding to the promoter. Further we also showed that high-mobility group box proteins (HMGBs) are sensors for wide variety of nucleic acids. Based on above findings, we further analyzed the detail mechanisms of the IL-12p40 gene regulation by IRF-3 and the role of HMGB1 in vivo. Since IL-12p40, component of both IL-12 and IL-23, is critical for the polarization of Th1- and Th17-type T cell responses, to clarify the regulatory mechanism of IL-12p40 is thought to be important to understand interaction between innate and adaptive immunity. It has been reported that IL-12p40 gene induction is controlled not only by promoter but also by cis-acting enhancer located on about 10 kbp upstream from transcription start site, which prompted us to examine whether the enhancer activity is also regulated by IRF-3 and/or IRF-5. By chromatin immunoprecipitation assay and enhancer-promoter reporter assay, we have found that the enhancer contains three interferon-stimulated response element (ISRE) sites and two of which is critical for the fulminant activation of the reporter gene. These data suggest that IRFs regulate the activation of

IL12p40 gene through not only the promoter but also the enhancer of the gene. Besides the role of nucleic acid sensor, HMGB1 is known to have multi-function. For instance, HMGB1 is released from the nucleus to the extracellular milieu upon cellular injury or inflammation, and the released HMGB1 functions as a proinflammatory cytokine. Thus, HMGB1 is thought to relate the pathological conditions of autoinflammation and autoimmunity. However, Hmgb1 knockout (KO) mice die soon after birth, the physiological function of HMGB1 has not been addressed so far. Recently, we have established Hmgb1 conditional KO (Hmgb1 cKO) mice. By using these mice, we are analyzing the role of HMGB1 in infectious and inflammatory disease models of mice. In this poster session, we will show our new data and want to discuss clinical implications of HMGB1 on infectious and inflammatory diseases.