

細胞性免疫誘導型ワクチンアジュバントの開発研究

石井 健 (医薬基盤研究所)

Adjuvant innovation by manipulation of innate immune system

Ken J ISHII, National Institute of Biomedical Innovation

1. Marichal T, Ohata K, Bedoret D, Mesnill C, Sabatell C, Kobiyama K, Lekeuxl P, Coban C, Akira S, Ishii KJ, Bureau F, Desmet CJ. (2011)

DNA released from dying host cells mediates aluminum adjuvant activity.

Nat Med, in press.

Aluminum-based adjuvants (alum) are widely used in human vaccination, although little is understood of their mechanisms of action. Here, we report that, in mice, alum causes the release of host cell DNA, which acts as a potent endogenous immunostimulatory signal mediating alum adjuvant activity. Furthermore, we show that host DNA signaling differentially regulates IgE and IgG1 production upon alum immunization. Indeed, we support that host DNA induces primary B cell responses, including IgG1 production, through IRF-3 independent mechanisms, and 'canonical' type 2 T cell responses associated with IgE isotype switching and effector tissue responses through IRF-3 dependent mechanisms. The finding that host cell DNA is a damage-associated molecular pattern relaying alum adjuvant activity may thus help in the comprehension of the mechanisms of action of current vaccines and in the design of novel adjuvants.

2. Kuroda E, Ishii KJ, Uematsu S, Ohata K, Coban C, Akira S, Aritake K, Urade Y, Morimoto Y. (2011)

Silica Crystals and Aluminum Salts Regulate the Production of Prostaglandin in Macrophages via NALP3 Inflammasome-Independent Mechanisms.

Immunity, 34: 514-526.

Particulates such as silica crystal (silica) and aluminum salts (alum) activate the inflammasome and induce the secretion of proinflammatory cytokines in macrophages. These particulates also induce the production of immunoglobulin E via a T helper 2 (Th2) cell-associated mechanism. However, the mechanism involved in the induction of type 2 immunity has not been elucidated. Here, we showed that silica and alum induced lipopolysaccharide-primed macrophages to produce the lipid mediator prostaglandin E(2) (PGE(2)) and interleukin-1 β (IL-1 β). Macrophages deficient in the inflammasome components caspase 1, NALP3, and ASC revealed that PGE(2) production was independent of the NALP3 inflammasome. PGE(2) expression was markedly reduced in PGE synthase-deficient (Ptges(-/-)) macrophages, and Ptges(-/-)mice displayed reduced antigen-specific serum IgE concentrations after immunization with alum or silica. Our results indicate that silica and alum regulate the production of PGE(2) and that the induction of PGE(2) by particulates controls the immune response in vivo.

3. Koyama S, Aoshi T, Tanimoto T, Kumagai Y, Kobiyama K, Tougan T, Sakurai K, Coban C, Horii T, Akira S, Ishii KJ. (2010)

Plasmacytoid dendritic cells delineate immunogenicity of influenza vaccine subtypes.

Sci Transl Med, 2: 25ra24.

A variety of different vaccine types are available for H1N1 influenza A virus infections; however, their immunological mechanisms of action remain unclear. Here, we show that plasmacytoid dendritic cells (pDCs) and type I interferon (IFN)-mediated signaling delineate the immunogenicity of live attenuated virus, inactivated whole-virus (WV), and split-virus vaccines. Although Toll-like receptor 7 acted as the adjuvant receptor for the immunogenicity of both live virus and WV vaccines, the requirement for type I IFN production by pDCs for the immunogenicity of the vaccines was restricted to WV. A split vaccine commonly used in humans failed to immunize naïve mice, but a pDC-activating adjuvant could restore immunogenicity. In blood from human adults, however, split vaccine alone could recall memory T cell responses, underscoring the importance of this adjuvant pathway for primary, but not secondary, vaccination.

4. Coban C, Igari Y, Yagi M, Reimer T, Koyama S, Aoshi T, Ohata K, Tsukui T, Takeshita F, Sakurai K, Ikegami T, Nakagawa A, Horii T, Nuñez G, Ishii KJ, Akira S. (2010)

Immunogenicity of whole-parasite vaccines against *Plasmodium falciparum* involves malarial hemozoin and host TLR9.

Cell Host Microbe, 7: 50-61.

Although whole-parasite vaccine strategies for malaria infection have regained attention, their immunological mechanisms of action remain unclear. We find that immunization of mice with a crude blood stage extract of the malaria parasite *Plasmodium falciparum* elicits parasite antigen-specific immune responses via Toll-like receptor (TLR) 9 and that the malarial heme-detoxification byproduct, hemozoin (HZ), but not malarial DNA, produces a potent adjuvant effect. Malarial and synthetic (s)HZ bound TLR9 directly to induce conformational changes in the receptor. The adjuvant effect of sHZ depended on its method of synthesis and particle size. Although natural HZ acts as a TLR9 ligand, the adjuvant effects of synthetic HZ are independent of TLR9 or the NLRP3-inflammasome but are dependent on MyD88. The adjuvant function of sHZ was further validated in a canine antiallergen vaccine model. Thus, HZ can influence adaptive immune responses to malaria infection and may have therapeutic value in vaccine adjuvant development.

5. Ishii KJ, Kawagoe T, Koyama S, Matsui K, Kumar H, Kawai T, Uematsu S, Takeuchi O, Takeshita F, Coban C, Akira S. (2008)

TANK-binding kinase-1 delineates innate and adaptive immune responses to DNA vaccines.

Nature, 451: 725-729.

Successful vaccines contain not only protective antigen(s) but also an adjuvant component that triggers innate immune activation and is necessary for their optimal immunogenicity. In the case of DNA vaccines, this consists of plasmid DNA; however, the adjuvant element(s) as well as its intra- and inter-cellular innate immune signalling pathway(s) leading to the encoded antigen-specific T- and B-cell responses remain unclear. Here we demonstrate in vivo that TANK-binding kinase 1 (TBK1), a non-canonical I κ B kinase, mediates the adjuvant effect of DNA vaccines and is essential for its immunogenicity in mice. Plasmid-DNA-activated, TBK1-dependent signalling and the resultant type-I interferon receptor-mediated signalling was required for induction of antigen-specific B and T cells, which occurred even in the absence of innate immune signalling through a well known CpG DNA sensor-Toll-like receptor 9 (TLR9) or Z-DNA binding protein 1 (ZBP1, also known as DAI, which was recently reported as a potential B-form DNA sensor). Moreover, bone-marrow-transfer experiments revealed that TBK1-mediated signalling in haematopoietic cells was critical for the induction of antigen-specific B and CD4(+) T cells, whereas in non-haematopoietic cells TBK1 was required for CD8(+) T-cell induction. These data suggest that TBK1 is a key signalling molecule for DNA-vaccine-induced immunogenicity, by differentially controlling DNA-activated innate immune signalling through haematopoietic and non-haematopoietic cells.