Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Homeostatic inflammation in innate immunity

Kensuke Miyake[1,2] and Tsuneyasu Kaisho[3,4,5]

Innate immune sensors respond not only to microbial products but also to endogenous metabolites such as nucleic acids (NAs) and lipids. Toll-like receptors (TLRs) deliver a signal from the plasma membrane and also from endolysosomes, where NAs and lipids are catabolized. Interaction of TLRs with metabolites in endolysosomes leads to homeostatic TLR activation. Dendritic cells expressing NA-sensing TLRs are steadily activated by metabolites derived from the host or commensals and produce type I IFNs, thereby provoking various types of inflammatory conditions. Here, we discuss how homeostatic inflammation is induced by innate immune sensors and is involved in maintaining immune homeostasis and causing non-infectious inflammatory diseases.

Addresses
[1] Division of Innate Immunity, Department of Microbiology and Immunology, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
[2] Laboratory of Innate Immunity, Center for Experimental Medicine and Systems Biology, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
[3] Laboratory for Inflammatory Regulation, RIKEN Center for Integrative Medical Sciences (IMS-RCAI), 1-7-22 Suehirocho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan
[4] Laboratory for Immune Regulation, World Premier International Immunology Frontier Research Center, Osaka University, 3-1 Yamadaoka, Suita, Osaka 565-0871, Japan
[5] Department of Immunology, Institute of Advanced Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama, Wakayama 641-8509, Japan

Corresponding authors: Miyake, Kensuke (kmiyake@ims.u-tokyo.ac.jp) and Kaisho, Tsuneyasu (tkaisho@ifrec.osaka-u.ac.jp)

Current Opinion in Cell Biology 2014, **30**:85–90

This review comes from a themed issue on **Effects of endogenous immune stimulants**

Edited by **Eicke Latz** and **Kensuke Miyake**

For a complete overview see the Issue and the Editorial

Available online 3rd September 2014

http://dx.doi.org/10.1016/j.coi.2014.08.003

Introduction

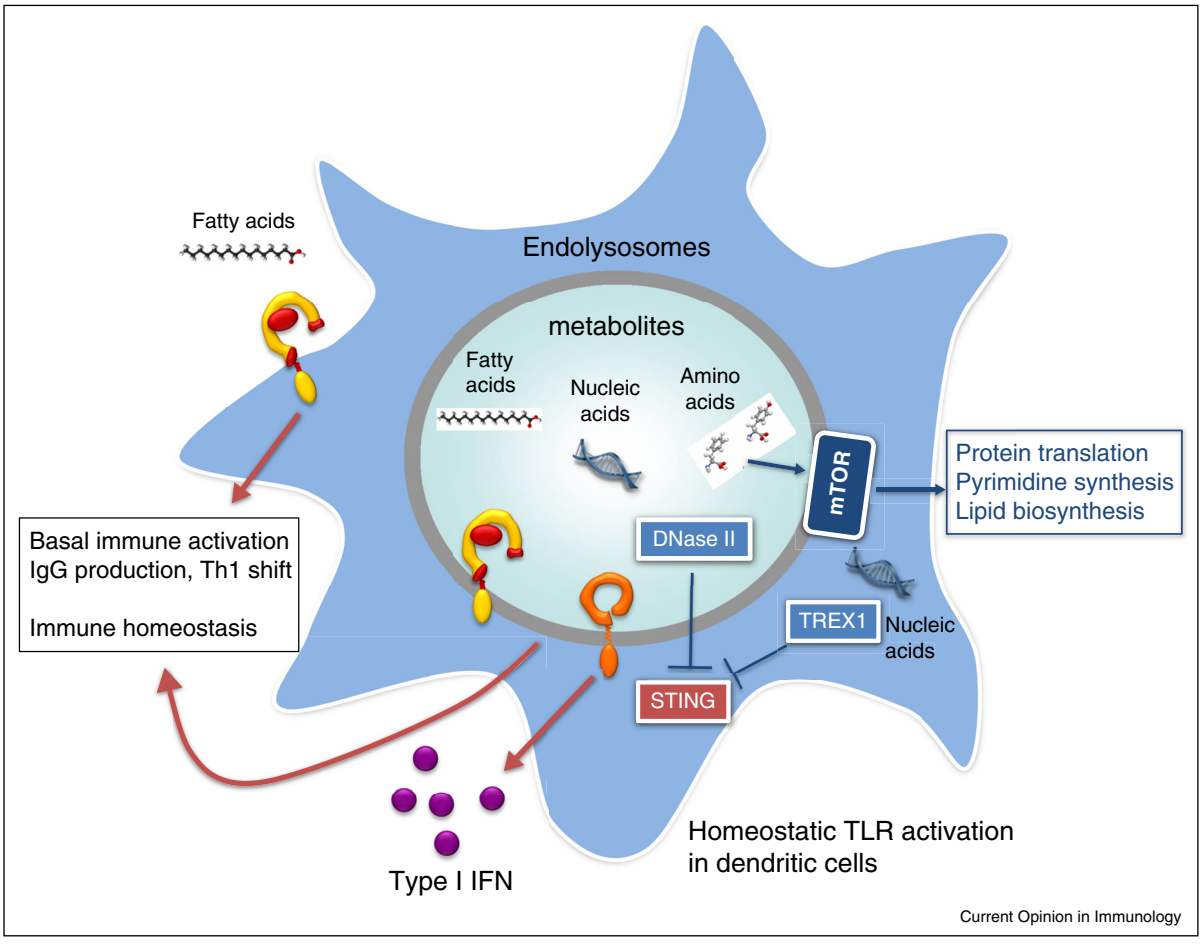
Self-pathogen discrimination continues to be the most important issue in immunology. The innate immune system is thought to have been evolutionally optimized to sense a group of pathogens, but not to react against self. Despite the optimization, Toll-like receptors (TLRs), the founding family of pathogen sensors, still react with self-derived products such as fatty acids, phospholipids, and nucleic acids (NAs), and have been implicated in a variety of autoimmune and non-infectious inflammatory diseases [1]. Receptors in the immune system including B cell receptors, T cell receptors, and NK receptors, all signal from the cell surface, and their signaling is terminated by their internalization. Meanwhile, certain Toll-like receptors (TLRs) are unique in this regard; the endotoxin sensor, TLR4/MD-2, and NA-sensing TLRs such as TLR3/7/8/9 are capable of signaling in the endolysosomes [2], where endogenous TLR ligands like fatty acids, phospholipids, and NAs are present as metabolites (Figure 1). Microbial sensing in the endolysosomes, therefore, takes the risk of reacting with self-derived products that are not yet 'a danger signal', but still metabolites.

Homeostatic TLR activation by endogenous metabolites may occur in the healthy state and even has a role in maintaining the integrity of the immune system. For example, antibody (Ab) production and T cell differentiation in the unperturbed state are altered by the lack of TLR signaling [3,4]. Notably, evidence is accumulating that certain metabolic diseases are influenced by a vicious circle driven by the interaction of pathogen sensors with endogenous metabolites. Pathologic inflammation in non-infectious inflammatory diseases can be understood as an outcome of uncontrolled homeostatic TLR activation. This article focuses on the interaction of TLRs with metabolites in dendritic cells (DCs) and macrophages at the steady and disease state and on the roles of DCs and macrophages in immune homeostasis.

Toll-like receptors respond to self-derived products

Toll-like receptors (TLRs) sense a variety of microbial products. Cell surface TLRs including TLR4/MD-2, TLR1/TLR2, TLR6/TLR2 recognize microbial membrane lipids, whereas TLR3, TLR7, TLR8, and TLR9 are localized to intracellular organelles and recognize microbial NAs [5–7]. MD-2 has a hydrophobic pocket that accommodates acyl chains of lipopolysaccharides [8]. However, the hydrophobic pocket of MD-2 can also accommodate fatty acids and saturated and unsaturated fatty acids are known to activate or inhibit TLR4/MD-2 signaling, respectively [9]. Of note, TLR4/MD-2 responses to fatty acids can drive chronic inflammation in fat tissue during obesity [10]. The end product of lipid oxidation, ω-(2-carboxyethyl) pyrrole (CEP), which is generated during inflammation and wound healing, can trigger TLR2 promoting angiogenesis [11]. Lipids are metabolized not only in cytoplasm but also in lysosomes

Figure 1



Endolysosome as a platform for innate immune and metabolic sensors. The endotoxin sensors, TLR4/MD2, and NA-sensing TLRs such as TLR3/7/8/9 are located in the endolysosome and trigger the signaling pathway leading to the production of type I IFNs. In the endolysosome not only many metabolites, which include the endogenous innate immune sensor ligands, but also metabolic sensors, such as mTOR, are present. Innate immune and metabolic sensor systems are intimately integrated together, which is exemplified by the finding that mTOR is crucially involved in TLR7/9-induced IRF-7 activation and type I IFN production as well as in TLR4/MD-2-induced IFN-β production. The cytoplasmic DNA sensors and the downstream signaling adaptor STING are also activated by accumulated DNAs to induce type I IFNs, although it remains unclear how those sensors crosstalk with the endolysosomal sensor systems. DNases negatively regulate activation of the STING pathway.

where they are transported through endocytosis or autophagic pathways [12]. The TLR4/MD-2 complex is furthermore able to activate type I IFN-inducing signal in endolysosomes [13,14].

TLR7 and TLR8 respond not only to single stranded RNA but also to nucleoside analogues such as imiquimod. It is possible that TLR7 and TLR8 respond to a physiological metabolite generated during RNA digestion. TLR3 can also respond to self-derived RNAs. Upon ultraviolet B (UVB) exposure noncoding self RNA is released from damaged keratinocytes and induces proinflammatory cytokines in a TLR3-dependent manner [15•]. In septic peritonitis and ischemic gut injury necrotic cells release NAs which are sensed by TLR3 and causing an inflammatory status [16•]. Furthermore, TLR3 is also involved in the pathogenesis of a gastrointestinal syndrome caused by high-dose ionizing radiation [17•]. Radiation induces cell damage and leakage of cellular RNA, which causes extensive cell death *via* TLR3 engagement. Thus, TLR3 is involved in the pathogenesis of several inflammatory responses by sensing self-derived NAs (Figure 2). Additionally, cytoplasmic DNA sensors are activated by self-derived DNA as described below.

Innate immune sensing by TLRs in endolysosomes

Type I interferon (IFN) is induced in endolysosomes by TLR4/MD-2 or TLR3/7/8/9 [13,18]. Considering the interaction between metabolites and TLRs in the