The subcellular dynamics of RNA stabilizing molecule in response to inflammation

~Inflammation is regulated by the balance of accelerator and brake~

Points

・Arid5a[*1)] contributes to augmentation of inflammatory cytokine serum levels *in vivo*.

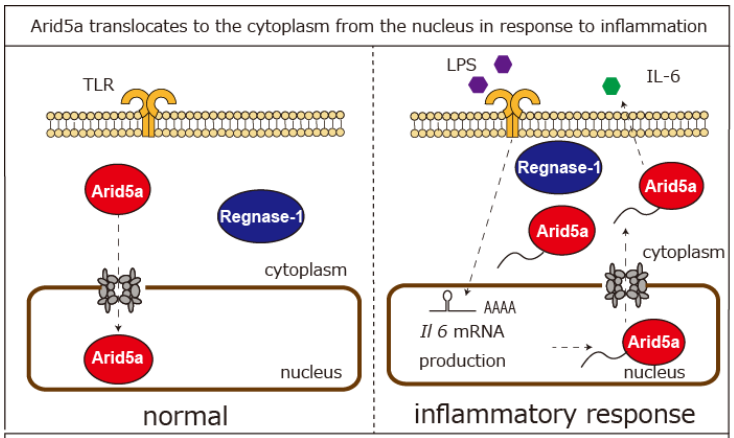
・Arid5a translocates to the cytoplasm from the nucleus in response to inflammation.

・The nucleocytoplasmic translocation of Arid5a is regulated by importin-α/β1 and CRM1.

・CRM1 Inhibitor, Leptomycin B, inhibited the nuclear export of Arid5a and IL-6[*2)] production after LPS stimulation.

Summary

Mitsuru Higa, Tadamitsu Kishimoto, and their research group revealed the regulatory mechanism of subcellular localization of Arid5a in response to inflammation. It has been known that an inflammatory accelerator, Arid5a, is localized in the nucleus, and an inflammatory brake, Regnase-1[*3)], is localized in the cytoplasm. In this study, they showed that 1) Arid5a translocates to the cytoplasm from the nucleus in response to inflammation, 2) bimax, which inhibit cNLS-dependent nuclear import via high-affinity interactions with NLS-binding sites of importin-α, inhibits the nuclear import of Arid5a, 3) CRM1 inhibitor, Leptomycin B, inhibits the nuclear export of Arid5a after LPS stimulation.



Model of inflammatory response by Arid5a/Regnase-1. Regnase-1 localizes to the cytoplasm. Arid5a is imported to the nucleus via an importin-α/β1 pathway. In response to inflammation, the Toll-like receptor (TLR) is activated by LPS, and *Il6* mRNA is induced by NF-κB. After that, Arid5a interacts with *Il6* mRNA and is exported to the cytoplasm.

Background

Macrophages produce inflammatory cytokines to active other immune cells and to exclude pathogens. However, over- or chronic inflammation causes diseases including a septic shock or autoimmunity. Therefore, the group has been studied the control mechanism of inflammation, especially focusing on the posttranscriptional regulation of the *Il6* mRNA by Arid5a and Regnase-1. Previous study showed that Arid5a binds to *Il6* mRNA 3′UTR to inhibit Regnase-1-mediated

RNA decay. Additionally, Arid5a deficient mice showed down-regulated inflammatory cytokine production, resistance to septic shock, and bleomycin-induced lung injury. Although Arid5a is known to play an important role in immune regulation, whether and how Arid5a subcellular localization impacts immune regulation has remained unclear.

Significance of the findings

The group showed that Arid5a translocates from the nucleus to the cytoplasm after LPS stimulation. Since the inhibition of Arid5a nuclear export causes the significant suppression of IL-6 production, further understanding of Arid5a dynamics may lead to novel therapeutic strategies of septic shock or autoimmune disease.

Technical terms

*1) AT-rich interactive domain 5a (Arid5a)

Arid5a is highly expressed in macrophages in response to lipopolysaccharide (LPS) and controls posttranscriptional regulation of IL-6 by stabilizing *Il6* mRNA by binding to its 3′ UTR

*2) Interleukin-6 (IL-6)

This is pro-inflammatory cytokine, is discovered by Kishimoto laboratory of Osaka University

*3) Regnase-1

Regnase-1 has been shown to destabilize *Il6* mRNA by interacting with a conserved stem-loop motif in the 3′ UTR

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Authors: Mitsuru Higa[a,b], Masahiro Oka[b], Yoshitaka Fujihara[c], Kazuya Masuda[a], Yoshihiro Yoneda[d] and Tadamitsu Kishimoto[a,1].

a) Laboratory of Immune Regulation, Immunology Frontier Research Center, Osaka University, Suita, 565-0871 Osaka, Japan

b) Laboratory of Nuclear Transport Dynamics, National Institutes of Biomedical Innovation, Health and Nutrition, Ibaraki, 567-0085 Osaka, Japan

c) Research Institute for Microbial Diseases, Osaka University, Suita, 565-0871 Osaka, Japan

d) National Institutes of Biomedical Innovation, Health and Nutrition, Ibaraki, 567-0085 Osaka, Japan

1) Corresponding author