Title
Toll-like receptor 4 antagonist TAK-242 inhibits autoinflammatory symptoms in DITRA

Key Points
- Deficiency of IL-36 receptor antagonist (DITRA) model mice has been established.
- The involvement of TLR4 signaling in the pathogenesis of DITRA was clearly demonstrated.
- Blockage of TLR4 signaling was shown as a promising treatment for DITRA.

Summary
Prof. Masashi Akiyama (corresponding author), Dr. Akitaka Shibata (first author) at Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) and Prof. Kazumitsu Sugiuara at Department of Dermatology, Fujita Health University School of Medicine proposed that toll-like receptor 4 antagonist TAK-242 inhibits autoinflammatory symptoms in DITRA

Generalized pustular psoriasis (GPP) and psoriasis vulgaris (PV) are variants of “psoriasis” which is an inflammatory skin disease with accelerated turnover of the epidermal keratinocytes. We reported that the majority of GPP without PV cases in Japanese are caused by mutations in IL36RN. IL36RN encodes IL-36 receptor antagonist (IL-36Ra), and loss-of-function mutations with autosomal recessive inheritance in IL36RN define a recessively inherited autoinflammatory disease, deficiency of IL-36 receptor antagonist (DITRA). In this context, GPP without PV is thought to be DITRA. IL36RN mutations are a major predisposing factor for DITRA, although certain triggering stimuli are probably needed for the onset of DITRA.

In this study, we established a model of autoinflammatory syndromes associated with DITRA, the cutaneous, hepatic, and articular lesions in Il36rn−/− mice via TLR4 activation, and successfully inhibited the onset of DITRA-related symptoms by using a selective TLR4 antagonist.

The present study clearly demonstrated that TLR4 signaling plays important roles in the onset of DITRA and inhibition of TLR4 signaling constitutes a promising treatment strategy for autoinflammatory symptoms associated with DITRA.

Our research findings were published in the scientific journal “The Journal of Autoimmunity” (electronic journal at February 11th in 2017).
**Research Background**

Generalized pustular psoriasis (GPP) and psoriasis vulgaris (PV) are variants of “psoriasis” which is an inflammatory skin disease with accelerated turnover of the epidermal keratinocytes. We reported that the majority of GPP without PV cases in Japanese are caused by mutations in \textit{IL36RN}. \textit{IL36RN} encodes IL-36 receptor antagonist (IL-36Ra), and loss-of-function mutations with autosomal recessive inheritance in \textit{IL36RN} define a recessively inherited autoinflammatory disease, deficiency of IL-36 receptor antagonist (DITRA). In this context, GPP without PV is thought to be DITRA. DITRA is a life-threatening disorder characterized by recurrent episodes of severe skin inflammation, with pustule development associated with fever, malaise, and extracutaneous involvement, including arthritis and neutrophilic cholangitis. \textit{IL36RN} mutations are thought to be a major predisposing factor for DITRA, although certain triggering stimuli are probably needed for the onset of DITRA.

In this study, we established a model of autoinflammatory syndromes associated with DITRA via TLR4 activation in \textit{Il36rn}^{-/-} mice and successfully inhibited the onset of DITRA-related symptoms by using a selective TLR4 antagonist.

**Research Results**

\textit{Il36rn}^{-/-} mice treated by LPS which is TLR4 agonist showed autoinflammatory symptoms in skin (Figure 1), liver (Figure 2) and articulation (Figure 3). Thus, we established model mice for DITRA or GPP that show cutaneous, articular, and hepatic autoinflammatory symptoms, sterile pustules on the skin, liver abscesses and enthesitis of the hind paws, typical of DITRA or GPP. Additionally, these symptoms were canceled by administration of a TLR4 antagonist, TAK-242. We demonstrated the inhibitory effects of the TLR4 antagonist TAK-242 on the autoinflammatory symptoms exhibited by the DITRA models.
Figure 1 Establishment and prevention of LPS-induced DITRA skin lesions in Il36rn−/− mice

LPS: TLR4 agonist
TAK-242: TLR4 antagonist
DWV: distilled water
Figure 2 Establishment and prevention of LPS-induced DITRA liver lesions in Il36rn−/− mice

LPS: TLR4 agonist
TAK-242: TLR4 antagonist
DW: distilled water
Research Summary and Future Perspective

Via TLR4-signaling activation, we established a model of the systemic autoinflammatory symptoms of DITRA, the cutaneous, hepatic, and articular lesions in \( \text{Il36rn}^{-/-} \) mice. In addition, we showed that the TLR4 antagonist TAK-242 prevents all three symptoms. These data suggest that inhibition of TLR4 signaling constitutes a promising treatment strategy for autoinflammatory symptoms associated with DITRA.

**Figure 3 Establishment and prevention of LPS-induced DITRA enthesitis in \( \text{Il36rn}^{-/-} \) mice**

**LPS**: TLR4 agonist  
**TAK-242**: TLR4 antagonist  
**DW**: distilled water
Publication

Akitaka Shibata, Kazumitsu Sugiura, Yasuhide Furuta, Yoshiko Mukumoto, Osamu Kaminuma and Masashi Akiyama.
Toll-like receptor 4 antagonist TAK-242 inhibits autoinflammatory symptoms in DITRA. *Journal of Autoimmunity*, Published online before print February 11th, 2017.

Japanese ver.