The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity.

Domínguez-Andrés J, Novakovic B, Li Y, Scicluna BP, Gresnigt MS, Arts RJW, Oosting M, Moorlag SJCFM, Groh LA, Zwaag J, Koch RM, Ter Horst R, Joosten LAB, Wijmenga C, Michelucci A, van der Poll T, Kox M, Pickkers P, Kumar V, Stunnenberg H, Netea MG (2019) The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity. *Cell Metab* 29(1), 211-220.e5.

Abstract

Sepsis involves simultaneous hyperactivation of the immune system and immune paralysis, leading to both organ dysfunction and increased susceptibility to secondary infections. Acute activation of myeloid cells induced itaconate synthesis, which subsequently mediated innate immune tolerance in human monocytes. In contrast, induction of trained immunity by β-glucan counteracted tolerance induced in a model of human endotoxemia by inhibiting the expression of immune-responsive gene 1 (IRG1), the enzyme that controls itaconate synthesis. β-Glucan also increased the expression of succinate dehydrogenase (SDH), contributing to the integrity of the TCA cycle and leading to an enhanced innate immune response after secondary stimulation. The

role of itaconate was further validated by IRG1 and SDH polymorphisms that modulate induction of tolerance and trained immunity in human monocytes. These data demonstrate the importance of the IRG1-itaconate-SDH axis in the development of immune tolerance and training and highlight the potential of β-glucan-induced trained immunity to revert immunoparalysis.

Involved units

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Details

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