Glucocorticoids limit acute lung inflammation in concert with inflammatory stimuli by induction of SphK1

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Abstract

Acute lung injury (ALI) is a severe inflammatory disease for which no specific treatment exists. As glucocorticoids have potent immunosuppressive effects, their application in ALI is currently being tested in clinical trials. However, the benefits of this type of regimen remain unclear. Here we identify a mechanism of glucocorticoid action that challenges the long-standing dogma of cytokine repression by the glucocorticoid receptor. Contrarily, synergistic gene induction of sphingosine kinase 1 (SphK1) by glucocorticoids and pro-inflammatory stimuli via the glucocorticoid receptor in macrophages increases circulating sphingosine 1-phosphate levels, which proves essential for the inhibition of inflammation. Chemical or genetic inhibition of SphK1 abrogates the therapeutic effects of glucocorticoids. Inflammatory p38 MAPK- and mitogen- and stress-activated protein kinase 1 (MSK1)-dependent pathways cooperate with glucocorticoids to upregulate SphK1 expression. Our findings support a critical role for SphK1 induction in the suppression of lung inflammation by glucocorticoids, and therefore provide rationales for effective anti-inflammatory

therapies.

Beteiligte Forschungseinheiten

Microbiome Dynamics Gianni Panagiotou Mehr erfahren

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Details

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