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SYSTEMIC LUPUS ERYTHEMATOSUS

Antihypertensive drug has dual effects

Guanabenz, an FDA-approved therapy for hypertension (and similar compounds) could be used for the treatment of interferon-dependent pathologies such as systemic lupus erythematosus (SLE), according to new findings. Treatment with guanabenz decreased the severity of autoimmune symptoms in a chemically induced model of SLE in mice, and also protected the mice from Toll-like receptor 9 (TLR9)-dependent cytokine shock.

"Our previous work on the cross-talk between endoplasmic reticulum stress and pathogen sensing has demonstrated the importance of protein phosphatase 1 regulatory subunit 15A (also known as GADD34) in anti-viral responses and dendritic cell (DC) activation, notably in type I interferon and pro-inflammatory cytokine production," explains co-corresponding author Philippe Pierre. "It was therefore natural to follow up on this work and test existing pharmacological inhibitors for their anti-inflammatory activity in vitro and in vivo using pathological mouse models."

> "Treatment with guanabenz decreased the severity of autoimmune symptoms in a chemically induced model of SLE"

In vitro, treatment of DCs with guanabenz, a proposed inhibitor of GADD34 activity, recapitulated the phenotype seen in DCs expressing a nonfunctional form of the gene encoding GADD34, and reduced pathogen-associated molecular pattern-induced production of type I interferon and other pro-inflammatory cytokines. Guanabenz also prevented the activation of TLR9, an important mediator of type I interferon production, independently of GADD34. Further analysis revealed that guanabenz blocked TLR9 signalling by inhibiting its transport to endosomes (where TLR9 is fully activated), an effect that was partially mediated by the inhibition of cholesterol 25-hydroxylase expression, an enzyme responsible for transforming cholesterol into 25-hydroxycholesterol (25-HC). Treatment of DCs with 25-HC reversed the inhibitory effects of guanabenz on TLR9 activation.

The agonistic activity of guanabenz, responsible for its antihypertensive effects, might be deleterious in certain patients, such as patients with SLE undergoing flares. "Several related compounds, such as sephin A, have recently been synthesized to eliminate this agonist activity, while conserving a proteostatic activity (GADD34 inhibition), and could be therefore used instead," remarks co-corresponding author Evelina Gatti. "In the future, we will attempt to understand better the mode of action of guanabenz, and of these alternative compounds, in the different cell types contributing to the inflammatory pathogenicity caused by different TLR agonists or type I interferon."

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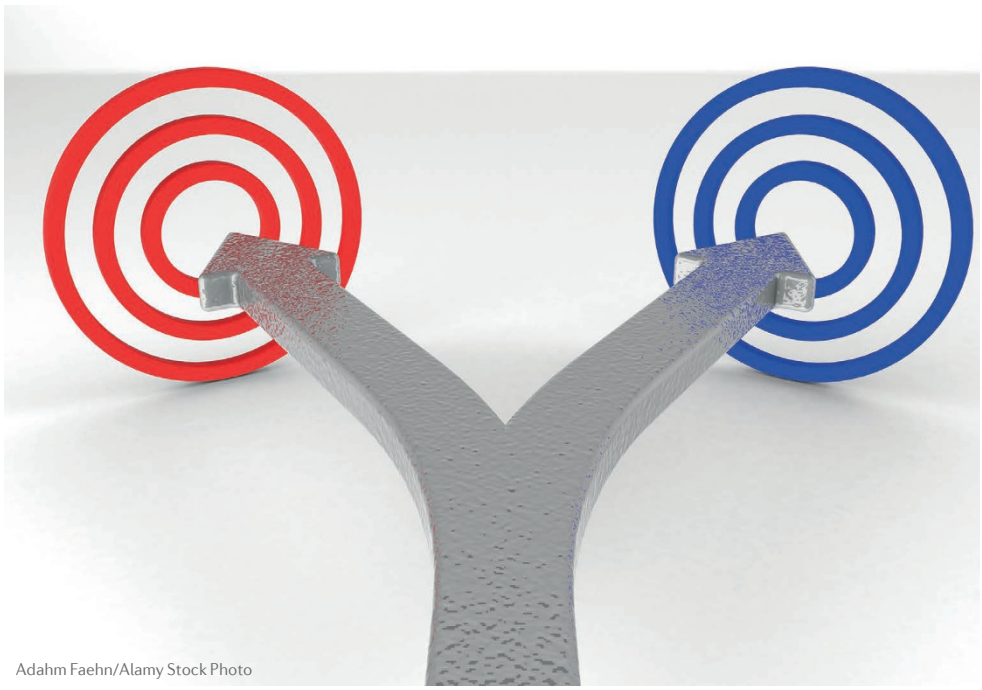

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ORIGINAL ARTICLE Perego, J. et al. Guanabenz inhibits TLR9 signaling through a pathway that is independent of eIF2α dephosphorylation by the GADD34/PP1c complex. *Sci. Signal.* https://doi.org/10.1126/scisignal.aam8104 (2018)