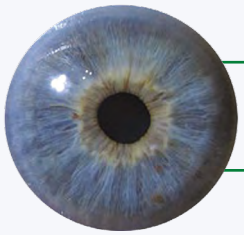

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Nitro-oleic acid regulates T cell activation through post-translational modification of calcineurin

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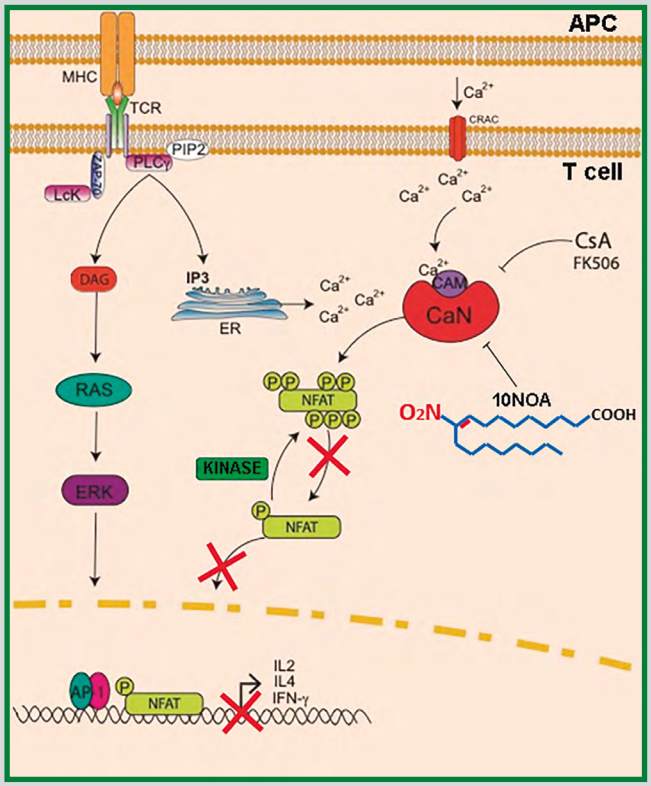
Nitro-fatty acids (NO_2-FAs), such as nitro-oleic acid (NO_2-OA), are electrophilic signalling molecules with cytoprotective and anti-inflammatory features detected in human urine and plasma. Under pathophysiological conditions NO_2-FAs are produced by the reaction of the nitric oxide-derived nitrogen reactive species, nitrogen dioxide and peroxynitrite, with unsaturated and conjugated FAs.



There are different mechanisms by which NO_2-FAs carry out their actions, however, electrophilic nitroalkylation of Cys is the main mechanism for their signalling activities. This reversible post-translational modification regulates protein function in different biological systems. For instance, nitroalkylation of transcription factors such as Keap1 results in increased expression of antioxidant response genes. In addition, NO_2-FAs exert positive and protective effects on a wide range of animal experi-

mental models of chronic inflammation where T lymphocytes and the activation of the immune system play a key role, such as psoriasis, allergic airway disease, allergic contact dermatitis, and inflammatory bowel disease.

In this work, we have shown that NO_2-OA modulates the activation of T lymphocytes, reducing the expression of the activation markers CD25 and CD71, IL-2 production and cell proliferation. In addition, NO_2-OA regulates the transcriptional activity mediated by NFAT, leading to a decrease in the induction of the expression of the cytokines IL-2, IFN-γ and IL4. We further found that the decrease in NFAT activation was due to the ability of NO_2-OA to inhibit the Ser/Thr phosphatase activity of calcineurin, leading to a reduction in NFAT dephosphorylation and translocation to the nucleus. By mass spectrometry assays, we observed that NO_2-OA nitroalkylates the catalytic subunit of calcineurin (CaNA), at Cys372, disturbing the functional formation of the CaNA/CaNB heterodimer, a mechanism by which NO_2-FAs could regulate the transcriptional activity of NFAT.

Altogether, our results suggest that NO_2-FAs may be potential immunomodulatory agents for the treatment of harmful T lymphocyte-mediated responses associated with autoimmune and allergic diseases.

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