INFLAMMASOME

Fishing for anti-inflammatory mechanisms

NPC

The benefits of a diet rich in fish oils — as exemplified by the low incidence of disorders such as type 2 diabetes in Greenland Eskimos — have been partly attributed to the anti-inflammatory effects of omega 3 (ω 3) fatty acids. The poorly understood mechanism responsible for these effects is now shown to involve direct inhibition of the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome.

When lipopolysaccharide-primed bone marrow-derived macrophages were pretreated with the ω 3 fatty acid docosahexaenoic acid (DHA), caspase 1 activation and the release of interleukin-1 β (IL-1 β) and IL-18 were inhibited in a dose-dependent manner in response to stimulation with an NLRP3 agonist. This effect was specific to ω 3 fatty acids — including eicosapentaenoic acid and α -linolenic acid — whereas various ω 6 and ω 9 fatty acids failed to block IL-1 β secretion. The inhibition of NLRP3 inflammasome activation by ω 3 fatty acids was confirmed in human THP1 macrophages and for various NLRP3 agonists. DHA also blocked caspase 1 activation and IL-1 β and IL-18 secretion in response to activation of the NLRP1B inflammasome, but it had no significant effect on NLRC4 (NOD-, LRR- and CARD-containing 4) or AIM2 (absent in melanoma 2) inflammasome activation.

“ ω 3 fatty acids can signal through GPR40–ARRB2 and/or GPR120–ARRB2 to inhibit ... inflammasome activation”

Oxygenated products of the ω 3 fatty acids, such as protectin D1 and resolvins D1, have been shown to have anti-inflammatory activity but they were not involved in ω 3 fatty acid-mediated inflammasome inhibition in this study. Instead, the authors showed that signalling through G protein-coupled receptor 40 (GPR40; also known as FFAR1) and GPR120 (also known as FFAR4) is required for the inhibition of inflammasome activation.

Pretreatment of macrophages with a small-molecule agonist of GPR40 and GPR120 had a similar inhibitory effect to DHA on the activation of the NLRP3 or the NLRP1B inflammasome. Furthermore, double deficiency of GPR40 and GPR120 in THP1 cells significantly relieved DHA-mediated inflammasome inhibition, as did deficiency of β -arrestin 2 (ARRB2), which is a downstream scaffold protein of GPR40 and GPR120. The results indicate that ω 3 fatty acids can signal through GPR40–ARRB2 and/or GPR120–ARRB2 to inhibit NLRP3 and NLRP1B inflammasome activation. ARRB2 was shown to bind to NLRP3 and to NLRP1B (but not to NLRC4 or to AIM2) in cotransfected cells, and treatment with DHA induced a GPR40- and GPR120-dependent interaction between NLRP3 and ARRB2 in THP1 cells.

The relevance of this mechanism to the negative regulation of the inflammasome was shown in a

mouse model of type 2 diabetes. Supplementation of mice fed a high-fat diet with DHA for 10 weeks prevented the development of insulin resistance and improved glucose tolerance. These beneficial effects of DHA were abrogated in *Nlrp3*^{−/−} mice, which shows that they depend on inhibition of the NLRP3 inflammasome. In support of this finding, liver and adipose tissue from mice fed a high-fat diet had higher levels of caspase 1 activation and IL-1 β and IL-18 production compared with mice fed a normal diet, but this metabolic stress-induced inflammasome activation could be blocked by DHA supplementation.

The results of this study describe a new mechanism for the anti-inflammatory effects of ω 3 fatty acids and for the negative regulation of inflammasome activation by the direct binding of ARRB2. Given the wide range of human pathologies now thought to involve inflammasome activation, the use of ω 3 fatty acids or the targeting of the GPR40–ARRB2 and/or GPR120–ARRB2 pathways could have broad clinical relevance.

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ORIGINAL RESEARCH PAPER Yan, Y. et al. Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. *Immunity* **38**, 1154–1163 (2013)

FURTHER READING Latz, E., Xiao, T. S. & Stutz, A. Activation and regulation of the inflammasomes. *Nature Rev. Immunol.* **13**, 397–411 (2013)

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Web summary: Omega 3 fatty acids negatively regulate inflammatory activation through a G protein-coupled receptor pathway.