Regulation of T lymphocyte functions by novel engineered polyunsaturated fatty acids

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Summary

Natural polyunsaturated fatty acids (PUFA) were synthesized and assessed as potential anti-inflammatory agents. β-oxa, β-thia and γ-thia PUFA were found to inhibit T lymphocyte responses *in vitro*, assessed as lymphoproliferation as well as production of tumour necrosis factor-β (TNFβ), interferon-γ (IFNγ) and interleukin-2 (IL-2). Threee of these compounds were studied in detail and found to be more active than the inhibition seen with fish oil fatty acid 22:6*n*-3. Interestingly these compounds unlike 22:6*n*-3 were poor stimulators of the human neutrophil respiratory burst, an additional advantage in their use as anti-inflammatory agents.

Examination of one of these three, β-oxa 21:3*n*-3, in *in vivo* models of chronic and acute inflammation showed that the fatty acids was highly inhibitory in both types of inflammatory responses. Thus the β-oxa 21:3*n*-3 inhibited the footpad swelling induced by sheep red blood cell antigens in a delayed type hypersensitivity (DTH) reaction as well as in the carrageenan-induced paw inflammation. This finding with DTH which is dependent on T lymphocytes is consistent with the ability of β-oxa 21:3*n*-3 to inhibit Th1 type cytokine production. While the reason for its effects on the carrageenan induced inflammation are less clear in this involves predominantly neutrophil infiltration, this reaction also has some T cell dependency. Studies on tissue distribution of the fatty acid, showed that β-oxa 21:3*n*-3 was incorporated into membrane phospholipids of liver and blood cells. Preliminary toxicology studies also demonstrated that β-oxa 21:3*n*-3 was well tolerated by the animals as several chemical and biochemical parameters of liver and kidney function remained within the normal range.

The mechanism of inhibition of T lymphocyte responses were in the main identified. The β-oxa 21:3*n*-3 acted at a post receptor level affecting signals modules critical for lymphocyte

activation and cytokine production. The fatty acid caused inhibition of PHA-PMA induced translocation of PKC-βI and PKC-ε, but not PKC-α, PKC-βII or PKC-θ. This was further delineated to show inhibition of downstream ERK pathway activation but not the JNK or p38 pathways.

This work has identified a new class of anti-inflammatory compounds which are based on PUFA. The action of the fatty acids is through the selective inhibition of the PKC-β1/ε and ERK signalling module.