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Previews

Aspirin-Triggered Metabolites of EFAs

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Aspirin triggers the biosynthesis of oxygenated metabolites from arachidonic, eicosapentaenoic, and docosahexaenoic (DHA) acids. In a preceding issue, Serhan et al. (2011) describe a novel aspirin-triggered DHA pathway for the biosynthesis of a potent anti-inflammatory and proresolving molecule.

Arachidonic (AA), eicosapentaenoic (EPA), and docosahexaenoic (DHA) acids are essential fatty acids (EFAs) that are required in human diet to supplement their endogenous production in humans. All three are characterized by being polyunsaturated with 4-6 nonconjugated *cis* double bonds and are generally identified either as omega-6 or omega-3 (Figure 1). These fatty acids are enzymatically released upon demand from their membrane-associated phospholipid precursors and serve as substrates for a number of key enzymes to produce a wide array of oxidative products that play major roles in regulating the immune function. The omega-3s DHA and EPA are enriched within the cell membranes of brain, retina, and testis where they are believed to have a protective role (Simopoulos, 1999). There is diverse and significant evidence that Western diets are deficient in these omega-3s, and this deficiency has been linked with many disease states. For this reason, they are widely supplemented in human diet with products based on marine oils and certain plants.

It is now well recognized that uncontrolled inflammation is associated with many diseases that are very prominent in Western populations, including arthritis, cardiovascular and respiratory diseases, as well as neurodegenerative conditions such as Alzheimer's and multiple sclerosis. Charles Serhan and his collaborators have identified potent oxidative products of DHA that he named resolvins, protectins, and maresins. These autacoids are locally synthesized in inflammatory exudates and were shown to have antiinflammatory and proresolving properties (Serhan et al., 2000, 2002). They are also produced in neural and brain tissues after injury (Serhan et al., 2000, 2002). Over the past decade, Serhan and coworkers have been able to structurally characterize these new products by combining careful synthetic chemistry structural analysis with insightful biological experiments.

A key feature associated with the discovery of the novel DHA oxidative metabolites is the role of aspirin in the biosynthesis of these molecules. Aspirin, the first chemically produced medication was synthesized in the 1850s and continues to be widely used for its analgesic and antiinflammatory properties. However, aspirin has also served as an invaluable pharmacological probe for unraveling several aspects of the inflammatory syndrome. First, during the 1970s, John Vane demonstrated that aspirin attenuates the biosynthesis of prostaglandins (Vane, 1982) by acting as an inhibitor of the enzyme cyclooxygenase-1 (COX-1). This discovery served as a basis for the development of a number of the widely used nonsteroidal antiinflammatory drugs (NSAIDs). In parallel, Samuelsson and coworkers identified a potent platelet-activating product biosynthesized from arachidonic acid. They named it thromboxane A_2 and showed that its production is also inhibited by aspirin (Samuelsson, 1982).

The pioneering work of Samuelsson and Vane led to the identification of several families of oxygenated products from arachidonic acid, represented by the prostaglandins, leukotrienes thromboxanes and lipoxins. Prostaglandins (PGs) and leukotrienes (LTs) are generally considered as pro-inflammatory where they participate in the first line of defense within the cell while lipoxins (LXs) serve as antiinflammatory mediators promoting resolution. Limiting the endogenous production of PGs and LTs has served as a basis for the development of antiinflammatory medications. The most successful of these, including aspirin, have targeted the enzyme cyclooxygenase-1 whose inhibition results in decreased levels of prostaglandins and thromboxanes.

A new aspect for aspirin's role in the biosynthesis of oxidative lipid modulators was recognized with the identification of the second eicosanoid oxidative enzyme cyclooxygenase-2 (COX 2), which is found abundantly in the vascular endothelium. It was shown that aspirin acts on this enzyme by acetylating its catalytic serine residue and prevents prostaglandin formation. However, although acetylated, the enzyme is still capable of other catalytic action producing a new product 15*R*-HETE, which is, in turn, converted by leukocytes to the potent antiinflammatory aspirin-triggered 15-*epi*-lipoxin A_4 which limits leukocyte entry into sites of inflammation (Takano et al., 1997). This finding followed the earlier observation by Serhan and collaborators (Clària and Serhan, 1995) that aspirin triggered the biosynthesis of novel lipid oxidative products identified as 15-*epi*-aspirin-triggered lipoxins. This novel enzymatic function for COX-2 is unique for this enzyme and not shown by COX-1. Structural studies attribute this enzymatic differentiation to the observation that unlike COX-1, the COX-2 catalytic domain is not entirely blocked by its aspirin-induced acetylation and is still capable of carrying out different enzymatic functions. In a human trial setting, Gilroy showed recently that aspirin triggers formation of lipoxins and limits the infiltration of leukocytes into the skin (Morris et al., 2009).

In a recent *Chemistry and Biology* report, Serhan and colleagues identified a proresolvin pathway involving DHA (Serhan et al., 2011). This work describes the chemical characterization of an aspirin-triggered neuroprotectin D1, a dihydroxy DHA product enzymatically produced in murine systems by isolated human

leukocytes. Unlike the structurally related normal DHA dihydroxylated product obtained by the action of lipoxygenase on DHA, in which the 17-OH has the *S*-absolute configuration, the new product which is produced by the aspirin-acetylated COX-2 enzyme has a 17*R*-OH configuration (Figure 1). Complete structural characterization was carried out by elegant synthetic and analytical work as with the earlier identified neuroprotectins (Marcheselli et al., 2010). This new protectin has potent antiinflammatory actions and stimulates resolution by activating macrophages and assists in clearing sites of inflammation by stimulating macrophages to uptake dead leukocytes and other cellular debris.

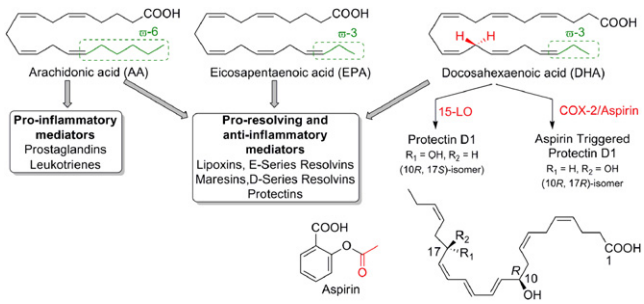

Figure 1. Products of Oxidative Transformations of Polyunsaturated Essential Fatty Acids

The structural characterization of these intriguing and very potent oxygenated lipid molecules coupled with the careful characterization of their immunomodulating properties opens the door for the development of novel therapeutics in the all-important field of inflammation. Characterization of the protein targets for these molecules is still at the early stages while correlation between their structures and activities is incomplete. Progress in these fronts should provide the basis for thoughtful target-based drug design to produce more biochemically stable and therapeutically targeted medications. Serhan's finding also suggests the combined use of DHA and aspirin as an attractive therapeutic avenue for the treatment of inflammatory conditions.

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PNA to DNA to Microarray Decoding Facilitates Ligand Discovery

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The development of a method for the amplification of PNA tags (Svensen et al., in this issue of *Chemistry & Biology*) should expand the range of biological targets amenable to screening using PNA-encoded combinatorial libraries and thus facilitate the discovery of new biologically useful agents.

The screening of libraries of molecules to identify those with desirable biological properties is fundamental to the drug discovery process and chemical biology studies in general. Solid-phase split-and-mix combinatorial synthesis techniques can rapidly generate libraries of vast numbers of compounds suitable for screening (Maclean et al., 1997; Harris and Winssinger, 2005; Díaz-Mochón et al., 2005). However, such libraries are obtained as complex mixtures, and determining the chemical identity of any individual biologically active member present is challenging. Toward this end, a number of chemical-encoding strategies have been developed where each molecule in the library becomes associated with (or incorporates) a unique tag encoding its unique synthetic history and thus molecular structure. This information can then