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Lipid mediators of inflammation in rheumatoid arthritis and osteoarthritis

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A B S T R A C T

Rheumatoid arthritis (RA) and osteoarthritis (OA) are inflammatory joint diseases, characterized by pain and structural damage. Besides prostaglandins, usually targeted by non-steroidal anti-inflammatory drugs, other lipids, including fatty acids, phospholipids and other bioactive lipid mediators derived from fatty acids could also contribute to RA and OA.

In this review, we present evidence for the role of fatty acids and derivatives in RA and OA by summarizing findings related to their presence in serum and synovial fluid, as well as their association with clinical characteristics and effects on RA and OA tissues in vitro. Finally, a more direct evidence for their role in RA and OA derived from intervention studies in humans or mouse models of disease is summarized. Based on the presented data, we present a research agenda, in which some key unresolved questions regarding the role of lipids in RA and OA are formulated.

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Introduction

Rheumatoid arthritis (RA) and osteoarthritis (OA) are joint diseases characterized by different pathophysiological mechanisms, but displaying common clinical characteristics, such as joint pain, functional impairment and structural damage which is hallmarked by bone erosions in RA and

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osteophytes in OA. Moreover, both diseases display joint space narrowing, reflecting cartilage loss. Another common feature of these diseases is the presence of inflammation in the majority of the patients. While the role of inflammation in the pathogenesis of RA has been established previously, its presence and possible role in OA has been only recently revealed. Several studies during the past 10 years have shown an association between synovial inflammation and pain on one hand and radiographic progression on the other hand, thus establishing the pivotal role of inflammation in OA (reviewed in Refs. [1,2]).

Fatty acids acquired through diet are usually transported through the body in triglycerides or phospholipids incorporated in lipoproteins, but can also be found in free form in blood. Moreover, they are present both in bound and free form in cells, where they perform various functions as energy source, membrane constituents or signalling molecules. They are the essential building blocks for higher-order lipids such as phospholipids, sphingolipids, glycerolipids and glycolipids. Moreover, they could be metabolized into bioactive lipid mediators such as oxylipins, including eicosanoids (prostaglandins, thromboxanes and leukotrienes) and other lipids with more anti-inflammatory and pro-resolving activity such as lipoxins, resolvins, maresins and protectins. Enzymes such as phospholipases (PLAs) which release fatty acids from phospholipids, cyclooxygenases (COXs) and lipoxygenases (LOXs) that oxidize fatty acids are involved in the generation of oxylipins. Fatty acids, higher-order lipids and oxylipins can interact with inflammatory as well as tissue-resident cells, thereby contributing to various processes in the body, including inflammation, wound healing, pain, etc, and potentially playing a role in RA and OA. In general, it is believed that saturated fatty acids, n-6 polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), and AA derivatives (prostaglandins and leukotrienes) have a pro-inflammatory effect. By contrast, unsaturated fatty acids, n-3 PUFA, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and the oxylipins derived from them (resolvins, maresins and protectins) are believed to have an anti-inflammatory function. The latter are also believed to be pro-resolving, thereby actively helping wound healing and return to tissue homeostasis after an inflammatory response.

In this review, we will present data supporting the role of lipids in RA and OA. To this end, we will summarize findings from three lines of evidence. First, data related to the presence of various fatty acids and their derivatives (lipid mediators) in blood or synovial fluid (SF) of RA and OA patients will be summarized. Next, the association of these lipids with clinical disease parameters will be presented, as well as in vivo intervention studies both in humans and mouse models of disease. Finally, in vitro studies indicating the effects of these lipids on human joint tissues will be presented (summarized in Fig. 1). The role of cholesterol and lipoprotein metabolism in RA and OA has been reviewed elsewhere [3,4] and will not be discussed in this review.

Lipids and lipid classes described in serum of healthy individuals

In an extensive study in which the major six lipid categories as defined by the Lipid Maps were measured in plasma of healthy individuals, more than 500 lipid species were identified [5]. The measured sample was obtained from the National Institute of Standards and Technology (USA); the pooled plasma sample was obtained and stored after overnight fasting in a standardized fashion, from 100 healthy individuals (age: between 40 and 50 years) including an equal number of men and women whose ethnicity was representative of the US population. The most abundant (on a molar basis) was sterols (including cholesterol), followed by triglycerides (part of lipoproteins), glycerophospholipids, free fatty acyls and sphingolipids, and the least abundant was diacylglycerols and prenols. In terms of free fatty acids, oleic acid, followed by palmitic acid and stearic acid were the most abundant and comprised approximately 78% of all free fatty acids after overnight fasting. The most abundant PUFA were linoleic acid (LA) and AA, but EPA and DHA, which are derived from fish oil and are known for their anti-inflammatory effects, were also detectable. Lipid mediators such as oxylipins were also detected in plasma, with 15-deoxy-PGD_2 (prostaglandin D2) being the major metabolite generated by COX, while 5-HETE was the most prominent eicosanoid of the LOX pathway found in plasma [5].

This review focuses on selected lipids in the six lipid classes: fatty acids either in free form or incorporated in higher-order lipids (especially phospholipids), as well as their bioactive lipid mediators in RA and OA (Table 1).

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