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Research paper

Resolvins as proresolving inflammatory mediators in cardiovascular disease

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ABSTRACT

Cardiovascular disease (CVD) represents a global burden with a prevalence that continues increasing progressively. CVD comprises a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease and peripheral arterial disease. This group of disorders is associated with an inflammatory process which can participate in the pathophysiology of these diseases. Inflammation resolution is an active process involving the participation of pro-resolving mediators such as lipoxins, resolvins, protectins and maresins. Pro-resolving mediators are bioactive molecules generated from omega-3 polyunsaturated fatty acids (PUFAs); among these eicosapentaenoic acid (EPA; C20:5n3) and docosahexaenoic acid (DHA; C22:6n3) are the precursors of resolvins. Pro-resolving mediators orchestrate the correct resolution of inflammation and also stimulate tissue regeneration. Their deregulation can lead to chronic inflammation involving CVD. The discovery of these novel lipid mediators opens a new range of possibilities for the design of anti-inflammatory agents with therapeutic potential for a wide variety of diseases. The present work summarizes the available data about the general characteristics, structure and biosynthesis of resolvins and their relation as protective compounds in CVD.

1. Introduction

Effective immune response pathways against pathogens constitute an essential requirement for survival living, and the functional factors that regulate key metabolic and immune processes in higher organisms have evolved from common ancestral structures, being evolutionarily conserved throughout species [35]. As a result, immune response is highly integrated with the metabolic regulation, and the proper function of each is intimately dependent on the other. For this reason, metabolic disorders are crucially linked to inflammatory events. This interface is considered a pivotal central homeostatic mechanism, dysfunction of which can lead to the development of a cluster of chronic metabolic disorders, concretely obesity, type 2 diabetes and cardiovascular disease. Currently, these diseases represent the greatest threat to the worldwide human health and welfare; in fact, coronary artery disease (CAD) remains to be the leading cause of death in the world [77]. There is extensive epidemiologic literature supporting the association between inflammation and CAD [18,77,102,105]. Current evidence supports that inflammatory cells and proteins, and inflammatory responses from vascular cells play a major role in the development and propagation of CAD, since they are major forces underlying the onset of coronary plaques, their unstable progression and eventual rupture.

The concept of inflammation and some of its satellite terms (such as acute and chronic) can be defined as a protective response of living tissues to local lesions. Inflammatory events include molecular, cellular and vascular phenomena addressed towards physical, chemical or biological aggressions [24,38,46]. Inflammation is characterized by cellular migration (extravasation) into the injured site that will trigger off the elimination or inhibition of the

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primary cause of damage, the clearance of necrotic cells and the initiation of the tissue repair. Both vasodilatation of closer blood vessels and an increased permeability facilitate the arrival of cellular and molecular mediators to the harmed spot [24,46]. Acute inflammation is the first response after a damaging stimulus. It takes place among toll-like receptors (TLR)-mediated infections, managed by the innate immune system, and it involves plasma and leukocytes (especially granulocytes) liberation into the injured tissue. Macrophages and mastocytes -resident in the injured tissue- are able to release soluble compounds that will eventually exert their effects on vascular permeability permitting the massive arrival of leukocytes (mainly neutrophils) and other molecules involved in inflammatory response. Afterwards, pathogent-contact or cytokines present in the scenario activated the neutrophils. A central point in the inflammatory process is the necessity to be actively finished when is no longer needed and this is accomplished by different mechanisms according with the affected tissue in order to avoid collateral damage [46]. Otherwise, an incorrect or inexistent resolution of inflammation can turn into a perpetuation of damage tissue and necrosis, which can result in chronic inflammation and developing a sustained pathological state [63]. Different biochemical events propagate and mature the inflammatory response, and multiple mediators are released, among which the following ones stand out: vaso-active amines and peptides (histamine, serotonin), fragments of the complement system (anafilotoxins), inflammatory cytokines (tumor necrosis factor alpha -TNFα-, interleukins -IL- 1 and 6), chemokines (IL-8), proteolytic enzymes (matalloproteinases, elastase) and lipid mediators (prostaglandins, thromboxanes, leukotrienes, lipoxins).

Lipids are potent signalling molecules that play an important role in homeostasis and host defence [5]; when inflammation occurs, phospholipids of membrane from activated cells of the immune system are metabolized to generate a wide variety of lipid substances which mediate the inflammatory response [86]. Stimuli such as injury, microorganisms or interleukin 8 activate Phospholipase A_2, which in turn generates free arachidonic acid (AA), a 20-carbon fatty acid and a leading precursor of lipid mediators. AA is easily metabolized via two principal pathways to form a family of oxygenated products called eicosanoids [49,94]. In addition, prostaglandins (PGs) and thromboxanes (TRX) are produced by ciclooxigenases (COX); leukotrienes (LTs) and lipoxines (LXs) are formed by lipooxigenases (LOXs). In recent years, several molecules derived from COX-2 oxidation of omega 3 fatty acids have been elucidated [88,89], and postulated to exert powerful resolving effect on inflammation. Resolvins, derived from the “resolution phase interaction products”, are endogenous bioactive lipid mediators that have been found to promote resolution of acute inflammation through interaction with high-affinity surface membrane receptors in human polymorphonuclear leukocytes [14,37,38,48].

2. Chemical structure of resolvins

As it has been introduced previously, resolvins are dihydroxy and trihydroxy metabolites of omega-3 fatty acids (Table 1). The characteristics and properties of a fatty acid depend on the length of the carbon chain but also on the presence or not of unsaturations. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) have multiple double bonds, with the first ones being on the carbon number 3 and 6, respectively, from the methyl end (omega carbon) of the hydrogen carbonate chain [95]. Mammals cannot synthesize all fatty acids because they cannot insert double bonds before carbon 9 in oleic acid (C18:1n9). More specifically, mammals

Table 1
Resolvins E and D classes and precursors. IUPAC names.

Resolvins E class precursors	
EPA	(5Z,8Z,11Z,14Z,17Z)-icosa-5,8,11,14,17-pentaenoic acid
18R-HEPE	(5Z,8Z,11Z,14Z,16E,18R)-18-hydroxyicosa-5,8,11,14,16-pentaenoic acid
5S-Hp-18R-HEPE	(5S,6E,8Z,11Z,14Z,16E,18R)-5-hydroperoxy-18-hydroxyicosa-6,8,11,14,16-pentaenoic acid
18S-HEPE	(5Z,8Z,11Z,14Z,16E,18S)-18-hydroxyicosa-5,8,11,14,16-pentaenoic acid
5S-Hp-18S-HEPE	(5S,6E,8Z,11Z,14Z,16E,18S)-5-hydroperoxy-18-hydroxyicosa-6,8,11,14,16-pentaenoic acid
18S-resolvins E class	
18S-RvE1	(5S,6Z,8E,10E,12R,14Z,16E,18S)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid
18S-RvE2	(5S,6E,8Z,11Z,14Z,16E,18S)-5,18-dihydroxyicosa-6,8,11,14,16-pentaenoic acid
18S-Rv3	(5Z,8Z,11Z,13E,15E,17R,18S)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid
18R-resolvins E class	
18R-RvE1	(5S,6Z,8E,10E,12R,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid
18R-RvE2	(5S,6E,8Z,11Z,14Z,16E,18R)-5,18-dihydroxyicosa-6,8,11,14,16-pentaenoic acid
18R-RvE3	(5Z,8Z,11Z,13E,15E,17R,18R)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid
Resolvins D class precursors	
DHA	(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid
17S-HpDHA	(4Z,7Z,10Z,13Z,15E,17S,19Z)-17-hydroperoxydocosa-4,7,10,13,15,19-hexaenoic acid
17S-HDHA	(4Z,7Z,10Z,13Z,15E,17S,19Z)-17-hydroxydocosa-4,7,10,13,15,19-hexaenoic acid
17R-HpDHA	(4Z,7Z,10Z,13Z,15E,17R,19Z)-17-hydroperoxydocosa-4,7,10,13,15,19-hexaenoic acid
17R-HDHA	(4Z,7Z,10Z,13Z,15E,17R,19Z)-17-hydroxydocosa-4,7,10,13,15,19-hexaenoic acid
17S-resolvins D class	
17S-RvD1	(4Z,7S,8R,9E,11E,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid
17S-RvD2	(4Z,7S,8E,10Z,12E,14E,16R,17S,19Z)-7,16,17-trihydroxydocosa-4,8,10,12,14,19-hexaenoic acid
17S-RvD3	(4S,5E,7E,9E,13Z,15E,17S,19Z)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid
17S-RvD4	(4S,6E,8E,10E,13E,15Z,17S,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15,19-hexaenoic acid
17R-resolvins D class or (aspirin-triggered; AT) resolvins D class	
17R-RvD1 or AT-RvD1	(4Z,7S,8R,9E,11E,13Z,15E,17R,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid
17R-RvD2 or AT-RvD2	(4Z,7S,8E,10Z,12E,14E,16R,17R,19Z)-7,16,17-trihydroxydocosa-4,8,10,12,14,19-hexaenoic acid
17R-RvD3 or AT-RvD3	(4S,5E,7E,9E,13Z,15E,17R,19Z)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid
17R-RvD4 or AT-RvD4	(4S,6E,8E,10E,13E,15Z,17R,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15,19-hexaenoic acid

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