Advances in Medical Sciences 63 (2018) 22–29

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Review article

A systematic review on the role of eicosanoid pathways in rheumatoid arthritis

Malvina Hoxha[a,b,*]

[a] Department of Chemical-Toxicological and Pharmacological Evaluation of Drugs, Catholic University Our Lady of Good Counsel, Tirana, Albania
[b] Department of Pharmacological and Biomolecular Sciences, Università degli studi di Milano, Milan, Italy

ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form 5 June 2017
Accepted 18 June 2017
Available online xxx

Keywords:
Rheumatoid arthritis
Inflammation
Arachidonic acid pathway
Prostaglandins
Leukotrienes

ABSTRACT

Background: Rheumatoid arthritis is characterized by the production of eicosanoids, cytokines, adhesion molecules, infiltration of T and B lymphocytes in the synovium and oxygen reduction accompanied by the cartilage degradation. Eicosanoids are responsible for the progressive destruction of cartilage and bone, however neither steroids, nor the non steroidal anti-inflammatory drugs (NSAIDs), cannot slow down cartilage and bone destruction providing only symptomatic improvement. The current rheumatoid arthritis treatment options include mainly the use of disease-modifying anti-rheumatic drugs, the corticosteroids, the NSAIDs and biological agents.

Methods: PubMed, Cochrane, and Embase electronic database were used as the main sources for extracting several articles, reviews, original papers in English for further review and analysis on the implication of arachidonic acid metabolites with rheumatoid arthritis and different strategies of targeting arachidonic acid metabolites, different enzymes or receptors for improving the treatment of rheumatoid arthritis patients.

Results: We first focused on the role of individual prostaglandins and leukotrienes, in the inflammatory process of arthritis, concluding with an outline of the current clinical situation of rheumatoid arthritis and novel treatment strategies targeting the arachidonic acid pathway.

Conclusions: Extended research is necessary for the development of these novel compounds targeting the eicosanoid pathway, by increasing the levels of anti-inflammatory eicosanoids (PGD_2,15dPGJ_2), by inhibiting the production of pro-inflammatory eicosanoids (PGE_2, LTB_4, PGI_2) involved in rheumatoid arthritis or also by developing dual compounds displaying both the COX-2 inhibitor/TP antagonist activity within a single compound.

Contents

Abbreviations: RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; AA, arachidonic acid; PG, prostaglandins; LT, leukotrienes; TX, thromboxanes; LX, lipoxins; NSAID, non steroidal anti-inflammatory drugs; COXIB, COX-2 selective inhibitors; TNF alpha, tumor necrosis factor alpha; IL-1, interleukin-1; IL-6, interleukin-6; IFN-γ, interferon gamma; HETE, hydroxyeicosatetraenoic acids; PLA_2, phospholipase A_2; TLRs, toll-like receptors; GPCR, G-protein coupled receptors; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinases; FLS, fibroblast-like synoviocytes; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; EULAR, European League Against Rheumatism; Th17, T helper 17; AP-1, activator protein 1; mPGES, membrane-associated prostaglandin E synthase; PGH_2, prostaglandin H_2; PGE_2, prostaglandin E_2; RASFs, rheumatoid arthritis synovial fibroblasts; PGES, prostaglandin E synthase; cPGES, cytosolic PGES; CIA, collagen induced arthritis; VEGF, vascular endothelial growth factor; PGD_2, prostaglandin D_2; PGDS, prostaglandin-D synthase; 15d-PGJ_2, 15-deoxy-D12,14-prostaglandin J_2; L-PGDS, lipocalin PGDS; H-PGDS, hematopoietic PGDS; PPAR-γ, peroxisome proliferative –activated receptor γ; PGI_2, prostacyclin; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; 8-*iso*-$PGF_{2\alpha}$, 8-*iso*-prostaglandin $F_{2\alpha}$; 15-LO, 15-Lipoxygenase; 5-LO, 5-lipoxygenase; 12-LOX, 12-lipoxygenase; CysLT, cysteinyl leukotrienes; LTB_4, leukotriene B_4; 15-(S)-HETE, 15-*S*-hydroxyeicosatetraenoic acid; PLGF, placenta growth factor; EETs, epoxyeicosatrienoic acids; DMARDs, disease-modifying antirheumatic drugs; CV, cardiovascular; LO inhibitors, lipooxygenase inhibitors.

* Corresponding author at: Department of Chemical–Toxicological and Pharmacological Evaluation of Drugs, Catholic University Our Lady of Good Counsel, Rruga Dritan Hoxha, Tirana, Albania.
E-mail address: malvis22@hotmail.com (M. Hoxha).

http://dx.doi.org/10.1016/j.advms.2017.06.004
1896-1126/

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune chronic inflammatory joints disorder that is characterized by an excessive synovial inflammation, proliferation, the formation of rheumatoid pannus and production of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), by synovial joint inflammation and consequently by destruction of bone and cartilage [1,2].

In the 1970s the synovial fluid of RA patients was analysed and higher prostaglandin (PG) levels were detected. Arachidonic acid (AA) pathway is complex and gives rise to the production of different AA metabolites such as prostaglandins (responsible of pain and swelling) [3], leukotrienes (LT), thromboxane (TX), lipoxins (LX), hydroxyeicosatetraenoic acids (HETE) which are involved in different inflammatory situations as rheumatoid arthritis and are responsible for the progressive destruction of cartilage and bone. Arachidonic acid metabolites are produced in inflamed synovium, inhibiting cell proliferation, and pannus formation in arthritis [4]. There are two isoforms of cyclo-oxygenases: COX-1 and COX-2 respectively. Specifically COX-2 is induced in inflammatory situations and is highly expressed in synovial tissues of patients with RA.

In addition, arachidonic acid metabolites can stimulate the activity of different cytokines (tumor-necrosis factor (TNF alpha)), interleukin-1/6 (IL-1, IL-6), chemokines (macrophage chemotactic peptide, interleukin 8 (IL-8)) or integrines [5]. TNF alpha is over expressed in rheumatoid arthritis pathogenesis, and together with interleukin-1 (IL-1), contribute to joint destruction in RA [6]. Macrophage migration inhibitory factor (MIF) is a cytokine that plays a key role in macrophage activation in RA [7]. IL-2, IL-12, IL-18, interferon gamma (IFN-γ), TNF-α, are secreted by the activated T cells and are produced in the synovial fluid and expressed in the synovial membrane, whereas IL-17 is produced by T helper 17 (Th17) and mast cells and found in synovial fluid of RA patients [8,9]. There is a further activation of Matrix metalloproteinases (MMP), responsible for the degradation of the cartilage, bringing to bone resorption [10]. The activation of fibroblast-like synoviocytes (FLS) in the inflamed synovium contribute to the production of different eicosanoids. Despite the proinflammatory cytokines in RA, there is also a production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β [11,12]. In summary, a number of cytokines, produced during inflammatory situations, are able to regulate eicosanoid metabolism such as: IL-1β enhances the PGE_2 production in synovial fibroblast [13]; IL-1β and TNFα enhance both the production of membrane-associated prostaglandin E synthase (mPGES-1) that is over expressed in synovium and cartilage contributing to the chronic inflammation present in RA [14], as well as of platelet type 12-lipoxygenase (12-LOX), which is expressed in human RA type B synoviocytes [15]. But from the other hand, cytokine activity is mediated and regulated by eicosanoids, for example: 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ_2) exerts a protective role in rheumatoid arthritis reducing the production of TNF alpha, and IL-6 [16–19], inhibiting the growth of synovial fibroblasts by apoptosis [20].

Currently there is an unmet clinical need for a novel rheumatoid arthritis treatment, ameliorating the existing strategies, which include mainly the use of disease-modifying antirheumatic drugs (DMARDs) such as: Gold salts, Methotrexate, Leflunomide, Azathioprine, Sulfasalazine, cyclosporine, cyclophosphamide etc; the non steroidal anti-inflammatory drugs (NSAID); the corticosteroids and biological agents (anti-TNFα agents (infliximab); anti-IL-6R, Rituximab etc). In addition, clinical trials have demonstrated benefits of fish oil rich in omega-3 fatty acids, in animal models of RA [21], reducing RA severity, improving the joint pathology [22–24], reducing the number of swollen joint, pain, morning stiffness, and total use of non steroidal anti-inflammatory drugs [25–27]. Despite the use of DMARD, and some beneficial effect of these drugs, such as of methotrexate, which has an anti-inflammatory action decreasing the inflammatory cytokines Il-1β, TNF alpha, macrophages, T cells, and probably prostaglandin E (PGE) release [28], the COX pathway still remains active. In the synovial fluid there is an overexpression of mPGES-1 and COX-2 [29]. From the other hand, corticosteroids are commonly used as powerful anti-inflammatory agents to suppress prostaglandin production in arthritis. Their use is associated with an increase of the cardiovascular (CV) risk, and with an impact on the metabolism, increasing body fat storage and fluid retention, therefore hypertensive patients and patients with diabetes should use corticosteroids cautiously. Dexamethasone is a glucocorticoid that reduces COX-2 and suppresses mPGES-1, probably by the interaction with nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and activator protein 1 (AP-1), two inducers of mPGES-1 [29–31]. The administration of intraarticular corticosteroids is followed by an abundant reduction in 5-LO expression leaving unaltered the 15-LO-1 enzyme, suggesting that corticosteroids reduce the formation of inflammatory metabolites in RA, and that 5-LO inhibitors can be used as an adjuvant therapy [32]. However, the benefit-risk profile of glucocorticoids is still a matter of debate and the latest European League Against Rheumatism (EULAR) recommendation suggest that glucocorticoids should be given as bridging therapy together with conventional synthetic DMARDs, either as part of the initial strategy or subsequently if this has failed, whereas when biological or targeted synthetic DMARDs are used, glucocorticoids are generally not needed. Moreover, glucocorticoids should be gradually reduced and ultimately stopped, ideally within 3–6 months [33,34].