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
Accepted 18 June 2017
Available online 14 August 2017

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].

2. Aim of the review

The aim of this review is to identify and synthesize all available information on the role of eicosanoid pathways in RA, and on the current and future therapeutic strategies for RA, targeting the enzymes or mediators generated within the eicosanoid pathways.

3. Methods

This review is conducted in line with the Prisma (Preferred Reporting Items for Systematic Reviews and meta-analyses) statement [35].

3.1. Literature search, data extraction

PubMed, Cochrane, and Embase electronic database were used as the main sources for extracting several articles, reviews, original papers, published in English for further review and analysis of the literature using as keywords the following: "Rheumatoid arthritis and arachidonic acid metabolites; or 'Rheumatoid arthritis and Prostaglandin D_2 (PGD_2)'; or "Rheumatoid arthritis and Prostaglandin E_2 (PGE_2)"; or "Rheumatoid arthritis and Prostaglandin J_2 (PGJ_2)"; or "Rheumatoid arthritis and Prostacyclin (PGI_2)"; or "Rheumatoid arthritis and Prostaglandin F_2 ($PGF_{2\alpha}$)"; or "Rheumatoid arthritis and 8-*iso*-$PGF_{2\alpha}$"; or "Rheumatoid arthritis and 5-lipoxygenase (5-LOX)"; or "Rheumatoid arthritis and 12-lipoxygenase (12-LOX)"; or "Rheumatoid arthritis and 15-lipoxygenase (15-LOX)"; or "Rheumatoid arthritis and cytochrome P450 epoxygenase pathway"; or "Rheumatoid arthritis and pro-resolving lipid mediators. The author of this review independently screened all these articles to identify those satisfying the inclusion criteria. The search process is reported in Fig. 1.

3.2. Eligibility criteria

Studies were considered eligible if they reported the role of different of AA mediators in RA conducted in both humans, and animals. The search was limited to the papers published in English, either reviews, cohort studies, case-control studies, randomized controlled trials. The articles were screened by titles or abstracts and the duplicated articles were excluded (Fig. 1).

4. Results

4.1. Overview of the literature search results

The initial search in Pubmed, Cochrane and Embase databases revealed 826 articles, which were all screened based on their titles and abstracts. Among all these studies 626 studies were excluded according to the eligibility criteria mentioned above. 200 studies were considered eligible and analysed for their quality and data content. 73 studies reported the implication of PGE_2 in RA (36.5%), 21 articles reported the role of leukotrienes and lipooxygenase pathway in RA (10.5%), 9 studies reported the role of PGJ_2 in RA (4.5%). All identified studies reporting the implication of $PGF_{2\alpha}$ or TXB_2 in the pathogenesis of RA (N = 5 in both cases) were performed in human synovial fluid. PGI_2 role in RA was reported in 7 articles of which 3 (42.85%) were performed in animal models of RA. Most studies showed that either, AA anti inflammatory mediators (PGD_2,15dPGJ_2) or AA pro- inflammatory mediators (PGE_2, LTB_4, PGI_2) are produced in RA. LTB_4 contributes to the amplification of the inflammatory response; in contrast to 15d-PGJ_2, which is responsible of the reduction of pro-inflammatory mediators such as interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNFα).

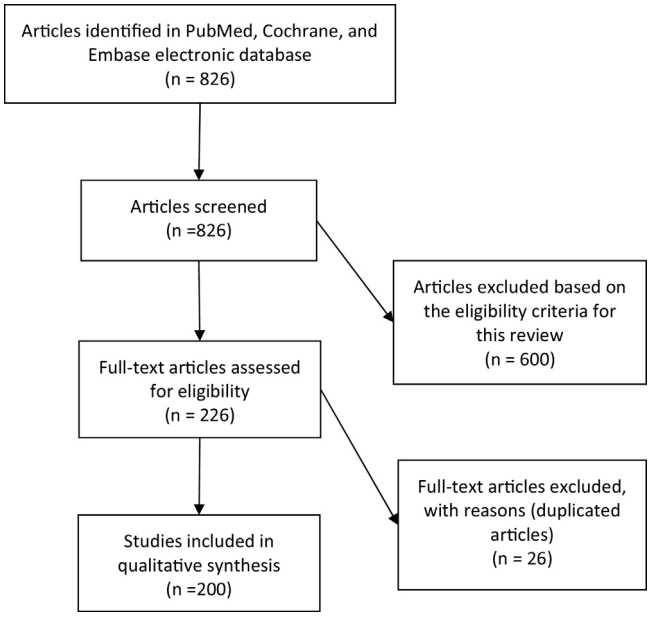

Fig. 1. Prisma flow diagram: schematic diagram of literature search and selection for articles included in this systematic review.

4.2. Synthesis of results

The results of the quality analysis for the identified studies are summarized below for each of the component of the arachidonic acid pathway correlated with RA.

4.2.1. Arachidonic acid pathway and RA

4.2.1.1. Phospholipase A_2. Phospholipase A_2 (PLA_2) catalyses the release of AA and the production of its metabolites, such as prostaglandins and leukotrienes involved in inflammation. High levels of PLA_2 are found in synovial tissue, provoking proliferative changes in synovial structures [36]. Type IIA phospholipase A_2 is secreted in the synovial fluid of patients with rheumatoid arthritis [37].

Toll-like receptors (TLRs) are a group of receptors involved in synovitis and joint destruction in RA and in particular TLR2 is found in excess in patients with RA, suggesting a potential role of TLR2 in joint destruction in RA [38]. Different studies demonstrate that TLR2 activate PLA_2 in synovial fibroblast-like cells.

4.2.1.2. Prostaglandin E_2. Prostaglandins play an essential role in vasodilatation and fluid extravasation in synovial tissues [39]. They bind to their G-protein coupled receptors (GPCR) with seven transmembrane domains.

mPGES is the enzyme responsible for the conversion of PGH_2 to PGE_2 in rheumatoid arthritis synovial fibroblasts (RASFs). Prostaglandin E synthase (PGES) is the enzyme responsible for the conversion of PGE_2, expressed in three different forms, respectively cytosolic PGES (cPGES), microsomal PGES-1 (mPGES-1) and mPGES-2, which are all detected in the synovial tissue of RA patients (Fig. 2). mPGES-1 has a inducible nature and is over expressed in synovium and cartilage contributing to the chronic inflammation, present in RA [14]. Genetic deletion of mPGES-1 reduces the incidence of collagen induced arthritis (CIA) [40].

PGE_2 is generated by chondrocytes and synovial fibroblasts, involved in synovial inflammation in RA [41]; however, data indicate that PGE_2 can have both pro and anti-inflammatory activities. PGE_2 exerts its action through EP1, EP2, EP3, and EP4 receptors, a group of GPCR, particularly coupled to Gi (for EP3

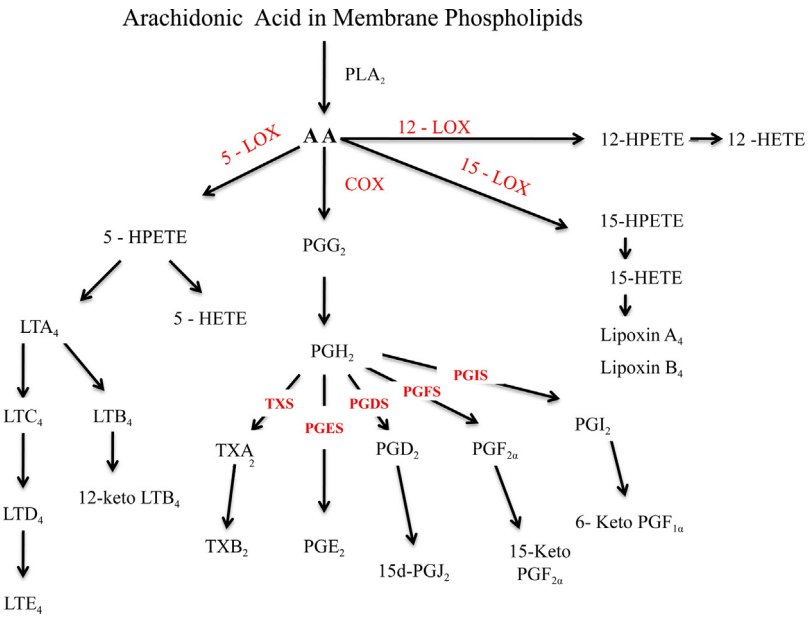

Fig. 2. Arachidonic acid pathway.
Arachidonic acid is a substrate for different pathways and enzymes giving rise to several metabolites. Prostaglandins and thromboxane are produced via the COX-pathway, unlike leukotrienes that are produced via 5-LO pathway. Abbreviations: phospholipase A_2 (PLA_2), arachidonic acid (AA), 5-lipoxygenase (5-LO), 15-Lipoxygenase (15-LO), 12-lipoxygenase (12-LOX), cyclooxygenase (COX), Prostaglandin G_2 (PGG_2), Prostaglandin H_2 (PGH_2), thromboxane synthase (TXS), thromboxane A_2 (TXA_2), thromboxane B_2 (TXB_2), Prostaglandin E synthase (PGES), Prostaglandin E_2 (PGE_2), Prostaglandin D synthase (PGDS), Prostaglandin D_2 (PGD_2), 15-deoxy-D12,14-prostaglandin J_2 (15d-PGJ_2), Prostaglandin F synthase (PGFS), Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 15-keto Prostaglandin $F_{2\alpha}$ (15-keto $PGF_{2\alpha}$), Prostaglandin I synthase (PGIS), Prostacyclin (PGI_2), 6-keto Prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$), 15-hydroperoxyeicosatetraenoic (15-HPETE), 15- hydroxyeicosatetraenoic acid (15-HETE), 12-hydroperoxyeicosatetraenoic (12-HPETE), 12-hydroxyeicosatetraenoic acid (12-HETE), 5-hydroperoxyeicosatetraenoic (5-HPETE), 5- hydroxyeicosatetraenoic acid (5-HETE), leukotriene A_4 (LTA_4), leukotriene B_4 (LTB_4), leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4), leukotriene E_4 (LTE_4), 12-keto leukotriene B_4 (12-keto LTB_4).

receptor), Gq (for EP1 receptor), Gs (EP2 and EP4). Moreover, PGE_2/EP4 play a proinflammatory role in the pathogenesis of rheumatoid arthritis [42], and through the activation of EP2 and EP4 receptor, PGE_2 regulates the cytokine production, vascular endothelial growth factor (VEGF), IL-6, etc. EP2 receptors are abundantly expressed in human articular cartilage [43] and PGE_2 exerts an anti-inflammatory action through the EP2. Instead, PGE_2 through EP4 receptor enhances type II collagen degradation, and therefore hypothesizing a potential role of EP4 antagonist in the treatment of RA [44,45]. Data demonstrate that PGE_2 is involved in complex interactions, bringing to articular cartilage erosions and juxta-articular bone [39]. Conventional NSAIDs and selective COX-2 inhibitors (COXIB) reduce the production of PGE_2, but still they are not the optimal approach for RA. In addition, microparticles, which are small vesicles that are released from activated or dying cells and that are found in the synovial fluid of RA patients, up-regulate the production of PGE_2 in synovial fibroblasts by inducing COX-2 and mPGES-1 [31].

4.2.1.3. Prostaglandin D_2. PGD_2 is produced by Prostaglandin D synthase and exerts its action by binding to two receptors, DP1 and CRTH2, respectively. PGD_2 is released by synovial fibroblast, osteoclasts, chondrocytes and mast cells in the synovial fluid [46–48]. PGD_2 exerts different functions: it enhances the chondrogenic differentiation, the type II collagen expression [49] and contributes to the cartilage maintenance and integrity [50,51]. However there is a rapid transformation of PGD_2 in PGs of the J series such as PGJ_2, δ12-PGJ_2, and 15d-PGJ_2. This latter is responsible of the anti-inflammatory effects attributed to the PGD_2, inhibiting different inflammatory mediators produced by macrophages/monocytes [52]. However, Maicas N. et.al [53] reported that PGD_2 produced during arthritis acts through the PGD_2 receptor, and plays an anti-inflammatory role [29].

4.2.1.4. 15-deoxy-D12,14-prostaglandin J_2 (15d-PGJ_2). 15d-PGJ_2 is an anti-inflammatory product of the AA pathway, a PGD_2 metabolite, which exerts a protective role in rheumatoid arthritis reducing the production of inflammatory mediators such as iNOS, TNFα, and IL-6 [16–19], inhibiting the growth of synovial fibroblasts by apoptosis [20]. From the two forms of PGDS (Prostaglandin-D synthase), respectively lipocalin PGDS (L-PGDS) and hematopoietic PGDS (H-PGDS), this latter is responsible for the production of 15d-PGJ_2. 15d-PGJ_2 activates the peroxisome proliferative −activated receptor γ (PPAR-γ), and is expressed in synovial fibroblasts in RA, inhibiting the expression of IL-1β and TNFα in synovial fibroblast. Furthermore, 15d-PGJ_2 inhibits mPGES-1 induction in IL-1β-synovial fibroblasts through the PPAR-γ pathway [54]. However, the role of 15d-PGJ_2 in rheumatoid arthritis still remains unclear due to different controversial studies showing the very limited biosynthesis of 15d-PGJ_2 in synovial fluid of patients with RA [41].

4.2.1.5. PGI_2. PGI_2 is produced by vascular endothelial cells and exerts its action through the IP receptor, mainly coupled to the Gs subunit. PGI_2 is a vasodilatator, and is abundantly found in synovial fluid in rheumatoid arthritis, acting as a proinflammatory lipid mediator [56,57]. 2,3,-dinor-6 keto-$PGF_{1\alpha}$, the main metabolite of PGI_2, was detected in the urinary levels of patients with RA. Moreover, in mice, treatment with PGI_2 receptor (IP) antagonist ameliorates the symptoms of CIA [58].

4.2.1.6. $PGF_{2\alpha}$. $PGF_{2\alpha}$ exerts its action through the G protein coupled receptor, the FP receptor, which is mainly coupled to the Gq subunit. Studies have reported the presence of $PGF_{2\alpha}$ in the urine of patients with RA [59], affirming that both inflammation and oxidative injury are part of the chronic inflammatory disease, such as RA.

4.2.1.7. 8-iso-prostaglandin $F_{2\alpha}$. 8-*iso*-prostaglandin $F_{2\alpha}$ (8-*iso*-$PGF_{2\alpha}$) is an isoprostane derived mainly by the free radical peroxidation of AA, and it is considered as a biomarker of the oxidative stress. Increased levels of 8-*iso*-$PGF_{2\alpha}$ have been found in RA and in different pathologies [60].

4.3. 5-LOX; 12-LOX; 15-LOX pathway in RA

AA can be a substrate for different enzymatic pathways, such as: 5-LOX, 12-LOX and 15-LOX. AA is metabolized by 5 LOX in LTA_4, LTB_4, LTC_4, and LTE_4 (Fig. 2). Both 15-Lipoxygenase (15-LO) and 5-lipoxygenase (5-LO) are expressed in RA synovium [32]. Liagre demonstrated that platelet type 12-lipoxygenase (12-LOX) is expressed in human RA type B synoviocytes [15], and its activity is enhanced by IL-1β and TNF-α.

Leukotrienes are important lipid mediators with a key role in the pathogenesis of inflammation. They are divided in two groups: leukotriene B_4 (LTB_4) and cysteinyl leukotrienes (CysLT: LTC_4, LTD_4, LTE_4), respectively. Specifically LTB_4 is a potent chemotactic arachidonic acid mediator, responsible of leukocyte recruitment and amplification of the inflammatory response. It is mainly produced by neutrophils, macrophages and mast cells [15,61] and is highly present in synovial fluid and serum of patients with active RA. LTB_4 enhances the neutrophil-dependent increased microvascular permeability [62] and exerts its activity by coupling to the LTB_4 G-protein coupled receptors, respectively BLT1 and BLT2. BLT1 was found in different cells as dendritic cells, osteoclasts and T cells. Furthermore BLT-1 deficient mice showed greatly reduced phenotypes in rheumatoid arthritis [63]. Data from Xu S et.al have demonstrated that LTB_4 contributes to RA through regulation of TNFalpha and IL1 beta, probably mediated by BLT2 receptor [64]. Moreover, it was demonstrated that in an autoantibody-induced inflammatory arthritis model, the $BLT2^{-}/^{-}$ mice showed reduced incidence and severity of RA, introducing a novel therapeutic target in treating inflammation in arthritis [65]. Despite the role of LTB_4 in RA, several studies have demonstrated no significant effect of LTB_4 receptor antagonist on RA, suggesting that LTB_4 does not play a major role in the inflammatory processes in RA [66].

Koshihara et.al. group demonstrated that other leukotrienes such as LTD_4, and LTE_4 were detected in synovial fluid in patients with RA [67], suggesting that the 5-LO pathway contributes to inflammatory processes in RA.

Lipoxins, instead have been shown to display anti-inflammatory properties. LXA_4 and 15-*epi*-LXA_4 exert their effects by binding to a G-protein coupled receptor, specifically ALXR, which is expressed in synovial fibroblast, and its activation brings to the resolution of inflammation [68], inhibiting the NF-kB in human leukocytes, and IL-6 expression in human synovial fibroblasts. LXA_4 has an essential role in the control and recruitments of neutrophils during inflammation [14]. Serhan et. al [69] demonstrated that LXA_4 protect rabbits from tissue damage, whereas other studies suggest that patients with anti-inflammatory drug therapy have higher levels of lipoxins, due to the long term benefits of the therapy [70]. Two isoforms of 15-LO were discovered, respectively 15 LO-1 isoform, was detected in synovial tissue, fibroblast and endothelial cells [32], whereas the 15-LO-2 has been found in infiltrating macrophages in human carotid plaques [71].

Evidences have demonstrated that 15−hydroxyeicosatetraenoic acid (15-HETE), generated by the 15-LOX, displays anti-inflammatory properties, reducing LTB_4 concentration in the synovial fluid [72], promoting osteoclastogenesis. However, different studies suggest a pro-inflammatory role of 15-LOX, by inhibiting the 5-LOX and 12-LOX enzyme activity [73]. Moreover, 15-S-hydroxyeicosatetraenoic acid (15-(S)-HETE), increased the expression of placenta growth factor expression (PLGF) in human rheumatoid arthritis.

4.4. Cytochrome P450 epoxygenase pathway and RA

The epoxyeicosatrienoic acids (EETs), are arachidonic acid metabolites catalyzed by cytochrome (CYP) P450 epoxygenases. Four epoxyeicosatrienoic acid (EET) regioisomers, 5,6-, 8,9-, 11,12-, and 14,15-EET, are formed and they function as lipid mediators, playing an important role in inflammation (Fig. 3). CYP2C and CYP2J enzymes are the principal isoforms that catalyze EETs formation [74]. From the other hand, CYP4 metabolize AA to 20-HETE. The EETs possess potent anti-inflammatory properties due to the suppression of NF-κB activation [75] and they are negatively correlated with different pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α), which instead promote bone resorption and osteoclastogenesis [76,77]. EETs inhibit osteoclastogenesis through different pathways and can be considered as a novel therapeutic strategy for osteoclast-related disorders, such as rheumatoid arthritis [77].

4.5. Pro-resolving lipid mediators

Resolving D5 and maresin 1 are two pro-resolving lipid mediators that derive from the omega-3 polyunsaturated fatty acids and display anti-inflammatory activity, reducing the joint damage and contributing to the resolution of inflammation. Lima −Garcia et.al, have demonstrated that 17 (R) HDoHE, a derivative of resolving D5 displays anti-hyperalgesic properties in CIA rats [78].

5. RA therapy and arachidonic acid metabolites: past, present and future

NSAIDs are used in rheumatoid arthritis to suppress inflammation and alleviate pain. They act by inhibiting COX, which is the enzyme responsible of the transformation of AA into different metabolites such as prostaglandins and thromboxane. Traditional NSAIDs, such as the gold standard aspirin were used to alleviate pain and suppress inflammation in many forms of arthritis. NSAIDs decrease the PGE_2 synthesis, however, currently not all NSAID are used for the treatment of RA. Traditional NSAIDs can cause gastrointestinal side effects such as gastric ulceration and bleeding, and all traditional NSAIDs other than aspirin are associated with increased cardiovascular risk [79].

COXIBs were developed to minimize the gastrointestinal risk associated with the use of traditional NSAIDs. COX-2 is highly induced in synovial tissues, mainly by IL-1 therefore after the development of COX-2 inhibitors (rofexocib, celecoxib,etericoxib) there were great expectation on these compounds. A body of evidence demonstrated an increase of cardiovascular risk in

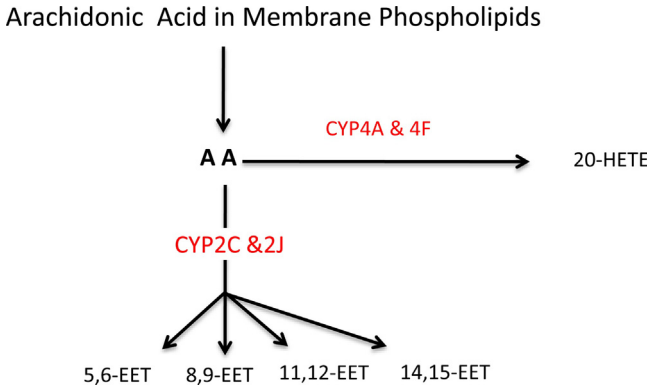

Fig. 3. The biosynthetic pathways for 20-HETE and EETs.

patients that were taking a COXIB in respect to those taking a conventional NSAID, leading to the market withdrawal of several COXIBs, limiting the use of COXIBs in RA patients, considering that the majority of these patients have also other risk factor, to develop myocardial infarction and ischemic stroke. Moreover, several studies have demonstrated that some non selective NSAIDs such as diclofenac and indomethacin, and celecoxib, a COX-2 selective inhibitor induce apoptosis in synovial fibroblast of RA patients, suggesting that they may also act as DMARD drugs other than displaying their traditional anti-inflammatory effect [80,81,14].

Considering that rheumatoid arthritis leads to oxidative stress and that traditional non steroidal anti-inflammatory drugs cannot stop the interaction of isoprostanes with the TXA_2 receptor (TPα receptor), produced in RA, a new innovative class of dual compounds with a double activity (COX-2 inhibitors/TP antagonist) can be considered as an alternative approach for patients with chronic inflammatory disease such as rheumatoid arthritis [82,83].

mPGES-1 is an important pharmacological target for the treatment of rheumatoid arthritis. Kojima group demonstrated that COX-2 inhibitors decrease PGE_2 production also by reducing mPGES expression in activated RASFs, however, as mentioned above, these compounds can give rise to cardiovascular events. Inhibitors of mPGES-1 may be an innovative treatment for rheumatoid arthritis, an alternative to non steroidal anti-inflammatory drugs, reducing PGE_2 production without affecting thromboxane and other prostaglandins levels. Considering that neither anti-TNF therapy, nor the B-cell depletion therapy such as rituximab could not suppress mPGES-1 or COX expression [84] the COX-mPGES pathway still remains active, hence targeting the PGE_2, by reducing its levels, or modulating the EP receptor signalling could be a potential RA treatment [14].

Different animal studies have demonstrated that retrovirally transfected PGDS cDNA, suppress the inflammatory responses, implying a potential role in the inflammatory disease such as rheumatoid arthritis [85].

Despite Kawahito et.al findings [20] that 15d-PGJ_2 suppresses inflammation in CIA, Bell-Parikh et.al [55] showed that in a group of six rheumatoid arthritis patients, 15d-PGJ_2 was not detected in the synovial fluid. However PGD_2 pathway can be a future therapeutic target for RA because of its anti-inflammatory effects.

Lipooxygenase inhibitors (LO inhibitors), could be a potential target for treating RA. LT antagonist can be used as anti-inflammatory therapy for rheumatoid arthritis. MK-886 is a LTB_4 synthesis inhibitor, and studies have shown a reduction of the pro-inflammatory cytokines, articular inflammation and joint destruction in a murine model of collagen induced arthritis [14,86]. As previously mentioned the findings of Mathis et.al have shown a reduction of the incidence and severity of RA in $BLT2^{-}/^{-}$ mice, which can bring to a new class of drugs to treat inflammation in RA by targeting BLT2 receptor. Despite that, there is a scarce experience with 5-LO and LTB_4 inhibitors in RA. Zileuton, a 5-LO inhibitor did not show any significant role in the improvement of the swollen joints in RA. Diaz- Gonzalez et.al demonstrated that treatment of RA patients with an oral long-acting LTB_4 receptor antagonist, BIIL 284 was modest, supporting the conclusion that LTB_4 is not a major inflammatory mediator in RA in humans [66].

Developing a hybrid drug, targeting both COX and 5-LOX activity was retained to be a satisfactory approach for treating RA. Tenidap was developed by Pfizer as COX/5-LOX inhibitor, but in 1996 FDA did not approve the use of Tenidap in RA, because of kidney and liver toxicity associated with the use of the drug.

Taken together, the findings of these studies suggest that targeting the eicosanoid pathway is important for the development of a novel class of drugs, however, the role of AA metabolites in RA needs further elucidation.

6. Conclusion

Despite the complexity of AA cascade, future therapeutic targets for RA should be directed towards the eicosanoid pathway.

Increasing the levels of anti-inflammatory AA mediators such as PGD_2, 15dPGJ_2, lipoxins, and inhibiting the production of pro-inflammatory eicosanoids, by using inhibitors of mPGES-1, PGE synthase, probably preventing cardiovascular diseases, can be an innovative approach for the treatment of rheumatoid arthritis.

From the other hand, developing a hybrid compound which can target at least two arachidonic acid pathway mediators, enzymes, or receptors could be a potential pharmacological approach for RA, such as a hybrid COXIB/TP antagonist compound. The NSAID story is a rise and fall story, and a third generation of NSAID could be of particular interest for RA patients. Nanocarriers, which are nanomaterials used for transporting another substance, can be useful in controlling the drug delivery to the inflamed synovium, reducing the bio distribution of anti-rheumatic drugs [87]. Further studies are needed to explore the implication of both proinflammatory and anti-inflammatory pathway in RA.

Despite the success of DMARDs and anticytokine therapy in rheumatoid arthritis there are still limiting factors such as: the safety concerns, high cost, treatment failure etc. The discovery of anti-cytokine therapy has provided greater possibility of controlling RA, although there are still problem on behalf. Rituximab, a biological agent did not reduce neither the expression of IL-6 and IL-1ß nor the levels of COX-1, COX-2 and m-PGES-1 [88], suggesting that the role of eicosanoids in RA is important for optimizing pharmacotherapy in patients with RA, maybe by using a potent antagonist of the PGE_2 production, or probably a hybrid COXIB/TP compound. Moreover, the administration of stabilized endogenous levels of EETs could represent a new pathway for RA, taking also in consideration that EETs also prevent the reactive oxygen species (ROS) production.

In summary, at this time we lack the ideal drug form RA patients and maybe by targeting the eicosanoid pathway we can reach the ultimate goal: to achieve the right drug, at the right dose, minimizing the side effects.

Financial disclosure

The author has no funding to disclose.

Conflict of interests

The author declare no conflict of interests.

References

[1] Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003;2(6):473–88.
[2] O'Dell JR, Smolen JS, Aletaha D, Robinson DR, Saint Clair EW. Rheumatoid arthritis. In: Stone JH, editor. A Clinician's Pearls and Myths in Rheumatology. . p. 1–13.
[3] Lee CM, Gupta S, Wang J, Johnson EM, Crofford LJ, Marshall JC, et al. Epithelium-specific Ets transcription factor-1 acts as a negative regulator of cyclooxygenase-2 in human rheumatoid arthritis synovial fibroblasts. Cell Biosci 20166(43), doi:http://dx.doi.org/10.1186/s13578-016-0105-7.
[4] Colantuoni G, Quintero M, Panasyuk A, Abderrahim L, Mitrovic DR. Do arachidonic acid and its metabolites, secreted by rheumatoid and osteoarthritic synovial tissue, account for the strong inhibition of DNA synthesis in cultured human articular chondrocytes? A novel approach to the mechanism of tissue damage. Joint Bone Spine 2005;72(6):533–9.
[5] Adam O. Dietary fatty acids and immune reactions in synovial tissue. Eur J Med Res 2003;8(8):381–7.
[6] Angel J, Colard O, Chevy F, Fournier C. Interleukin-1-mediated phospholipid breakdown and arachidonic acid release in human synovial cells. Arthritis Rheum 1993;36(2):158–67.
[7] Sampey AV, Hall PH, Mitchell RA, Metz CN, Morand EF. Regulation of synoviocyte phospholipase A2 and cyclooxygenase 2 by macrophage migration inhibitory factor. Arthritis Rheum 2001;44(6):1273–80.

[8] Su Z, Yang R, Zhang W, Xu L, Zhong Y, Yin Y, et al. The synergistic interaction between the calcineurin B subunit and IFN-γ enhances macrophage antitumor activity. Cell Death Dis 2015;6:e1740.
[9] Chimenti MS, Triggianese P, Conigliaro P, Candi E, Melino G, Perricone R. The interplay between inflammation and metabolism in rheumatoid arthritis. Cell Death Dis 2015;6(9):e1887.
[10] Steiner G, Tohidast-Akrad M, Witzmann G, Vesely M, Studnicka-Benke A, Gal A, et al. Cytokine production by synovial T cells in rheumatoid arthritis. Rheumatology (Oxford) 1999;38:202–13.
[11] Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 1996;14:397–440.
[12] Richardson D, Pearson RG, Kurian N, Latif ML, Garle MJ, Barrett DA, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid Arthritis. Arthritis Res Ther 2008;10(2):R43, doi:http://dx.doi.org/10.1186/ar2401.
[13] Bondeson J. Effects of tenidap on intracellular signal transduction and the induction of proinflammatory cytokines: a review. Gen Pharmacol 1996;27 (6):943–56.
[14] Kojima F, Kapoor M, Kawai S, Crofford LJ. New insights into eicosanoid biosynthetic pathways: implications for arthritis. Expert Rev Clin Immunol 2006;2:277–91.
[15] Liagrea B, Vergneb P, Rigauda' M, Beneytouta JL. Expression of arachidonate platelet-type 12-lipoxygenase in human rheumatoid arthritis typeB synoviocytes. FEBS Lett 1997;414(1):159–64.
[16] Kansanen E, Kivela AM, Levonen AL. Regulation of Nrf2-dependent gene expression by 15-deoxy-Delta12,14-prostaglandin J2. Free Radic Biol Med 2009;47:1310–7.
[17] Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature 1998;391:79–82.
[18] Waku T, Shiraki T, Oyama T, Morikawa K. Atomic structure of mutant PPARgamma LBD complexed with 15d-PGJ2: novel modulation mechanism of PPARgamma/RXRalpha function by covalently bound ligands. FEBS Lett 2009;583:320–4.
[19] Buckner MMC, Antunes LCM, Gill N, Russell SL, Shames SR, Finlay BB. 15-Deoxy-Δ12, 14-Prostaglandin J2 inhibits macrophage colonization by salmonella enterica serovar typhimurium. PLoS One 2013;8(7):e69759, doi:http://dx.doi.org/10.1371/journal.pone.0069759.
[20] Kawahito Y, Kondo M, Tsubouchi Y, Hashiramoto A, Bishop-Bailey D, Inoue KI, et al. 15-deoxy-Δ 12, 14-PGJ 2 induces synoviocyte apoptosis and suppresses adjuvant-induced arthritis in rats. J Clin Invest 2000;106(2):189–97.
[21] Calder PC. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. Biochim Biophys Acta 2015;1851(4):469–84, doi:http://dx.doi.org/10.1016/j.bbalip.2014.08.010.
[22] Leslie CA, Gonnerman WA, Ullman MD, Hayes KC, Franzblau C. Cathcart ES: Dietary fish oil modulates macrophage fatty acids and decreases arthritis susceptibility in mice. J Exp Med 1985;162:1336–9.
[23] Volker DH, FitzGerald PEB, Garg ML. The eicosapentaenoic to docosahexaenoic acid ratio of diets affects the pathogenesis of arthritis in Lew/SSN rats. J Nutr 2000;130:559–65.
[24] Ierna M, Kerr A, Scales H, Berge K, Griinari M. Supplementation of diet with krill oil protects against experimental rheumatoid arthritis. BMC Musculoskelet Disord 2010;11:136.
[25] Calder PC. PUFA, inflammatory processes and rheumatoid arthritis. Proc Nutr Soc 2008;67:409–18.
[26] Calder PC. w-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol 2013;75(3):645–62, doi:http://dx.doi.org/10.1111/j.1365-2125.2012.0437.
[27] James M, Proudman S, Cleland L. Fish oil and rheumatoid arthritis: past, present and future. Proc Nutr Soc 2010;69(03):316–23.
[28] Vergne P, Liagre B, Bertin P, Cook-Moreau J, Treves R, Beneytout JL, et al. Methotrexate and cyclooxygenase metabolism in cultured human rheumatoid synoviocytes. J Rheumatol 1998;25(3):433–40.
[29] Korotkova M, Jakobsson PJ. Persisting eicosanoid pathways in rheumatic diseases. Nat Rev Rheumatol 2014;10(4):229–41.
[30] Stichtenoth DO, Thoren S, Bian H, Peters-Golden M, Jakobsson PJ, Crofford LJ. Microsomal prostaglandin E synthase is regulated by proinflammatory cytokines and glucocorticoids in primary rheumatoid synovial cells. J Immunol 2001;167:469–74.
[31] Jüngel A, Distler O, Schulze-Horsel U, Huber LC, Ha HR, Simmen B, et al. Microparticles stimulate the synthesis of prostaglandin E2via induction of cyclooxygenase 2 and microsomal prostaglandin E synthase 1. Arthritis Rheum 2007;56:3564–74, doi:http://dx.doi.org/10.1002/art.22980.
[32] Gheorghe KR, Korotkova M, Catrina AI, Backman L, Af Klint E, Claesson HE, et al. Expression of 5-lipoxygenase and 15-lipoxygenase in rheumatoid arthritis synovium and effects of intraarticular glucocorticoids. Arthritis Res Ther 2009;11(3):R83, doi:http://dx.doi.org/10.1186/ar2717.
[33] Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidonysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs : 2016 update. Ann Rheum Dis 2017, doi:http://dx.doi.org/10.1136/annrheumdis-2016-210715.
[34] Buttgereit F, Bijlsma JW. Glucocorticoids in rheumatoid arthritis: the picture is shaping up. Ann Rheum Dis 2017, doi:http://dx.doi.org/10.1136/annrheumdis-2017-211187.
[35] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche P, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.A.
[36] Bostan M, Galatiuc C, Hirt M, Constantin MC, Brasoveanu LI, Iordachescu D. Phospholipase A2 modulates respiratory burst developed by neutrophils in patients with rheumatoid arthritis. J Cell Mol Med 2003;7:57–66, doi:http://dx.doi.org/10.1111/j.1582-4934.2003.tb00203.x.
[37] Massaad C, Paradon M, Jacques C, Salvat C, Bereziat G, Berenbaum F, et al. Induction of secreted type IIA phospholipase A2 gene transcription by interleukin-1β ROLE OF C/EBP FACTORS. J Biol Chem 2000;275(30):22686–94.
[38] Sommerfelt RM, Feuerherm AJ, Skuland T, Johansen B. Cytosolic phospholipase A2 modulates TLR2 signaling in synoviocytes. PLoS One 2015;10(4):e0119088.
[39] Stańczyk J, Kowalski ML. The role of cyclooxygenase and prostaglandins in the pathogenesis of rheumatoid arthritis. Pol Merkur Lekarski 2001;11(65):438–43.
[40] Trebino CE, Stock JL, Gibbons CP, Naiman BM, Wachtmann TS, Umland JP, et al. Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase. Proc Natl Acad Sci U S A 2003;100(15):9044–9.
[41] Martel-Pelletier J, Pelletier JP, Fahmi H. Cyclooxygenase-2 and prostaglandins in articular tissues. Semin Arthritis Rheum 2003;33(3):155–67.
[42] McCoy JM, Wicks JR, Audoly LP. The role of prostaglandin E2 receptors in the pathogenesis of rheumatoid arthritis. J Clin Invest 2002;110:651–8.
[43] Aoyama T, Liang B, Okamoto T, et al. PGE2 signal through EP2 promotes the growth of articular chondrocytes. J Bone Miner Res 2005;20(3):377–89.
[44] Attur M, Al-Mussawir HE, Patel J, Kitay A, Dave M, Palmer G, et al. Prostaglandin E2 exerts catabolic effects in osteoarthritis cartilage: evidence for signaling via the EP4 receptor. J Immunol 2008;181(7):5082–8.
[45] Otsuka S, Aoyama T, Furu M, et al. PGE2 signal via EP2receptors evoked by a selective agonist enhances regeneration of injured articular cartilage. Osteoarthritis Cartilage 2009;17(4):529–38.
[46] Gallant MA, Samadfam R, Hackett JA, Antoniou J, Parent J-L, Brum-Fernandes AJ. Production of prostaglandin D2 by human osteoblasts and modulation of osteoprotegerin, RANKL, and cellular migration by DP and CRTH2 receptors. J Bone Miner Res 2005;20:672–81, doi:http://dx.doi.org/10.1359/JBMR.04121.
[47] Pietila P, Moilanen E, Seppala E. Differences in the production of arachidonic acid metabolites between healthy and rheumatic synovial fibroblasts in vitro. A preliminary study. Scand J Rheumatol 1984;13(3):243–6.
[48] De Paulis A, Marinò I, Ciccarelli A, De Crescenzo G, Concardi M, Verga L, et al. Human synovial mast cells. I. Ultrastructural in situ and in vitro immunologic characterization. Arthritis Rheum 1996;39:1222–33, doi:http://dx.doi.org/10.1002/art.1780390723.
[49] Jakob M, Demarteau O, Suetterlin R, Heberer M, Martin I. Chondrogenesis of expanded adult human articular chondrocytes is enhanced by specific prostaglandins. Rheumatology (Oxford) 2004;43:852–7, doi:http://dx.doi.org/10.1093/rheumatology/keh197.
[50] Zayed N, Afif H, Chabane N, et al. Inhibition of interleukin-1β-induced matrix metalloproteinases 1 and 13 production in human osteoarthritic chondrocytes by prostaglandin D 2. Arthritis Rheum 2008;58(11):3530–40.
[51] Zayed N, Li X, Chabane N, et al. Increased expression of lipocalin-type prostaglandin synthase in osteoarthritic cartilage. Arthritis Res Ther 200810 (6).
[52] Mohammad JF, Abbas M. Prostaglandins and rheumatoid arthritis. Arthritis 2012, doi:http://dx.doi.org/10.1155/2012/239310 Article ID 239310, 7 pages.
[53] Maicas N, Ibáñez L, Alcaraz MJ, Ubeda A, Ferrándiz ML. Prostaglandin D2 regulates joint inflammation and destruction in murine collagen-induced arthritis. Arthritis Rheum 2012;64(1):130–40.
[54] Cheng S, Afif H, Martel-Pelletier J, Pelletier JP, Li X, Farrajota K, et al. Activation of peroxisome proliferator-activated receptor γ inhibits interleukin-1β-induced membrane-associated prostaglandin E2 synthase-1 expression in human synovial fibroblasts by interfering with Egr-1. J Biol Chem 2004;279 (21):22057–65.
[55] Bell-Parikh LC, Ide T, Lawson JA, McNamara P, Reilly M, FitzGerald GA. Biosynthesis of 15-deoxy-Δ 12, 14-PGJ 2 and the ligation of PPARγ. J Clin Invest 2003;112(6):945–55.
[56] Brodie MJ, Hensby CN, Parke A, Gordon D. Is prostacyclin the major pro-inflammatory prostanoid in joint fluid? Life Sci 1980;27:603–8.
[57] Dorris SL, Peebles RS. PGI2 as a regulator of inflammatory diseases. Mediators Inflamm 2012, doi:http://dx.doi.org/10.1155/2012/926968 Article ID 926968.
[58] Pulichino AM, Rowland S, Wu T, et al. Prostacyclin antagonism reduces pain and inflammation in rodent models of hyperalgesia and chronic arthritis. J Pharmacol Exp Ther 2006;319(3):1043–50.
[59] Łuczaj W, Gindzienska-Sieskiewicz E, Jarocka-Karpowicz I, Andrisic L, Sierakowski S, Zarkovic N, et al. The onset of lipid peroxidation in rheumatoid arthritis: consequences and monitoring. Free Radic Res 2016;50 (3):304–13, doi:http://dx.doi.org/10.3109/10715762.2015.1112901.
[60] Basu S, Whiteman M, Mattey DL, Halliwell B. Raised levels of F2-isoprostanes and prostaglandin F2α in different rheumatic diseases. Ann Rheum Dis 2001;60(6):627–31.
[61] Lewis RA, Austen KF, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway: biochemistry and relation to pathobiology in human diseases. N Engl J Med 1990;323:645–55.
[62] Brain SD, Williams TJ. Leukotrienes and inflammation. Pharmacol Ther 1990;46(1):57–66.
[63] Yokomizo T. Two distinct leukotriene B4 receptors, BLT1 and BLT2. J Biochem 2015;157(2):65–71, doi:http://dx.doi.org/10.1093/jb/mvu078.

[64] Xu S, Lu H, Lin J, Chen Z, Jiang D. Regulation of TNFalpha and IL1beta in rheumatoid arthritis synovial fibroblasts by leukotriene B4. Rheumatol Int 2010;30(9):1183–9, doi:http://dx.doi.org/10.1007/s00296-009-1125-y.
[65] Mathis SP, Jala VR, Lee DM, Haribabu B. Nonredundant roles for leukotriene B4 receptors BLT1 and BLT2 in inflammatory arthritis. J Immunol 2010;185 (5):3049–56, doi:http://dx.doi.org/10.4049/jimmunol.1001031.
[66] Díaz-González F, Alten RH, Bensen WG, Brown JP, Sibley JT, Dougados M, et al. Clinical trial of a leucotriene B4 receptor antagonist, BIIL 284, in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66(5):628–32.
[67] Koshihara Y, Isono T, Oda H, Karube S, Hayashi Y. Measurement of sulfopeptide leukotrienes and their metabolism in human synovial fluid of patients with rheumatoid arthritis. Prostaglandins Leukot Essent Fatty Acids 1988;32:113–9.
[68] Serhan CN, Chiang N. Lipid-derived mediators in endogenous anti-inflammation and resolution: lipoxins and aspirin-triggered 15-epi-lipoxins. Sci World J 2002;2:169–204.
[69] Serhan CN, Jain A, Marleau S, Clish C, Kantarci A, Behbehani B, et al. Reduced inflammation and tissue damage in transgenic rabbits overexpressing 15-lipoxygenase and endogenous anti-inflammatory lipid mediators. J Immunol 2003;171(12):6856–65.
[70] Thomas E, Leroux JL, Blotman F, Chavis C. Conversion of endogenous arachidonic acid to 5, 15-diHETE and lipoxins by polymorphonuclear cells from patients with rheumatoid arthritis. Inflamm Res 1995;44(3):121–4.
[71] Hulten LM, Olson FJ, Åberg H, Carlsson J, Karlström L, Borén J, et al. 15-Lipoxygenase-2 is expressed in macrophages in human carotid plaques and regulated by hypoxia-inducible factor-1Å. Eur J Clin Invest 2010;1:11–7.
[72] Fogh K, Hansen ES, Herlin T, Knudsen V, Henriksen TB, Ewald H, et al. 15-Hydroxy-eicosatetraenoic acid (15-HETE) inhibits carragheenan-induced experimental arthritis and reduces synovial fluid leukotriene B 4 (LTB 4). Prostaglandins 1989;37(2):213–28.
[73] Vanderhoek JY, Bryant RW, Bailey JM. Inhibition of leukotriene biosynthesis by the leukocyte product 15-hydroxy-5,8,11,13-eicosatetraenoic acid. J Biol Chem 1980;255:10064–6.
[74] Capra V, Bäck M, Barbieri SS, Camera M, Tremoli E, Rovati GE. Eicosanoids and their drugs in cardiovascular diseases: focus on atherosclerosis and stroke. Med Res Rev 2013;33.2:364–438.
[75] Node K, Huo Y, Ruan X, Yang B, Spiecker M, Ley K, et al. Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. Science 1999;285.5431:1276–9.
[76] Xu X, Zhang XA, Wang DW. The roles of CYP450 epoxygenases and metabolites, epoxyeicosatrienoic acids, in cardiovascular and malignant diseases. Adv Drug Deliv Rev 2011;63.8:597–609.
[77] Guan H, Zhao L, Cao H, Chen A, Xiao J. Epoxyeicosanoids suppress osteoclastogenesis and prevent ovariectomy-induced bone loss. FASEB J 2014;14–262055, doi:http://dx.doi.org/10.1096/fj.14-262055fj.
[78] Lima-Garcia JF, Dutra RC, Da Silva KABS, Motta EM, Campos MM, Calixto JB. The precursor of resolvin D series and aspirin-triggered resolvin D1 display anti-hyperalgesic properties in adjuvant-induced arthritis in rats. Br J Pharmacol 2011;164(2):278–93.
[79] Pawlosky N. Cardiovascular risk: are all NSAIDs alike? Can Pharm J/Revue des Pharmaciens du Canada 2013;146.2:80–3.
[80] Yamazaki R, Kusunoki N, Matsuzaki T, Hashimoto S, Kawai S. Nonsteroidal anti-inflammatory drugs induce apoptosis in association with activation of peroxisome proliferator-activated receptor gamma in rheumatoid synovial cells. J Pharmacol Exp Ther 2002;302(1):18–25.
[81] Kusunoki N, Ito T, Sakurai N, Suguro T, Handa H, Kawai S. A novel celecoxib derivative potently induces apoptosis of human synovial fibroblasts. J Pharmacol Exp Ther 2005;314(2):796–803.
[82] Bertinaria M, MAAG Shaikh, Buccellati C, Cena C, Rolando B, Lazzarato L, et al. Designing multitarget anti-inflammatory agents: chemical modulation of the lumiracoxib structure toward dual thromboxane antagonists–COX-2 inhibitors. ChemMedChem 2012;7:1647–60, doi:http://dx.doi.org/10.1002/cmdc.201200272.
[83] Hoxha M, Buccellati C, Capra V, Garella D, Cena C, Rolando B, et al. In vitro pharmacological evaluation of multitarget agents for thromboxane prostanoid receptor antagonism and COX-2 inhibition. Pharmacol Res 2016;103:132–43, doi:http://dx.doi.org/10.1016/j.phrs.2015.11.012.
[84] Gheorghe KR, Thurlings RM, Westman M, Boumans MJ, Malmström V, Trollmo C, et al. Prostaglandin E 2 synthesizing enzymes in rheumatoid arthritis B cells and the effects of B cell depleting therapy on enzyme expression. PLoS One 2011;6(1):e16378.
[85] Ando M, Murakami Y, Kojima F, et al. Retrovirally introduced prostaglandin D2 synthase suppresses lung injury induced by bleomycin. Am J Respir Cell Mol Biol 2003;28(5):582–91, doi:http://dx.doi.org/10.1165/rcmb.2002-0162OC.
[86] Sawazaki Y. Leukotriene B4, leukotriene C4 and prostaglandin E2 in the serum, synovial fluid and synovium in patients with rheumatoid arthritis. Nihon Ika Daigaku Zasshi 1989;56(6):559–64.
[87] Gouveia VM, Lima SCA, Nunes C, Reis S. Non-biologic nanodelivery therapies for rheumatoid arthritis. J Biomed Nanotechnol 201511(10) 1701-1721(21)..
[88] Gheorghe KR, Thurlings RM, Westman M, Boumans MJ, Malmström V, Trollmo C, et al. Prostaglandin E 2 synthesizing enzymes in rheumatoid arthritis B cells and the effects of B cell depleting therapy on enzyme expression. PLoS One 2011;6.1:e16378.