Published in final edited form as:

Inflamm Res. 2018 July ; 67(7): 589–596. doi:10.1007/s00011-018-1153-8.

Prostaglandin E2 and IL-23 interconnects STAT3 and RoR γ pathways to initiate Th17 CD4⁺ T-cell development during rheumatoid arthritis

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Abstract

Background—The chronic inflammation associated with rheumatoid arthritis (RA) leads to focal and systemic bone erosion of the joints resulting in a crippling disability. Recent reports indicate an increase in the incidence of RA in the coming years, placing a significant burden on healthcare resources. The incidence of RA is observed to be increasing with age and a significant proportion of those new cases will be aggressively erosive.

Findings—The altered physiology, due to immune disturbances, contributes towards RA pathogenesis. The imbalance of inflammatory cytokines and non-cytokine immune modulators such as prostaglandin E2 (PGE2) and IL-23-induced pathogenic IL-17, plays a crucial role in persistent inflammation and bone degradation during RA. However, the molecular mechanism of IL-23, a key cytokine and PGE2 in the development and perpetuation of IL-17 producing effector Th17 cells is poorly understood.

Conclusion—This review focuses on research findings that provide insight to the contribution of PGE2 and IL-23 during the development of pathogenic Th17 cells. We also highlight the key transcriptional factors required for Th17 development and therapeutic strategies to disrupt the interaction between IL-23 and IL-17 to prevent the end-organ damage in RA.

Keywords

Rheumatoid arthritis; autoinflammation; bone erosion; prostaglandin E2; IL-17; IL-23; Th17; RANKL; STAT3 and RoR γ

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Competing Interest: The authors declare no competing financial interests.

Author contributions: JS, LH, equally contributed in collecting the data and drafting the manuscript. ML, KY, WC, AM collected the data and drafted the manuscript. AI and DN collected the data. RS designed and wrote the manuscript.

Background

Inflammatory responses are generally required to resolve and repair tissue damage. However, dysfunction of the inflammatory response and its persistence can lead to loss of organ function. Under such conditions, inflammation may predispose to development of an autoimmune condition causing excessive tissue damage [1]. Rheumatoid arthritis (RA) is characterized as a chronic, autoinflammatory disorder resulting in abnormal degradation of the metatarsophalangeal and interphalangeal joints of the hand, wrist, feet, knee, shoulder, ankle, and hip [2]. The inflammatory response that characterizes RA is the single most important aspect of the disease and is responsible for aggravating the aforementioned bone deformities and disabilities. Upon activation, inflammatory cells at the site of inflammation release inflammatory mediators along with matrix degrading enzymes. This converts the synovial membrane into an inflammatory pannus that invades the joints and bones [2]. These abnormal autoinflammatory responses result in extreme vasodilation, migration of immune cells, muscle erosion with tendon rupture, swelling of the synovial membrane and fluid accumulation [3]. These studies suggest that inflammation is an important factor contributing to the detrimental effects of RA.

Two major pathways have been proposed to demonstrate the pathogenesis of RA [4]. First, anti-IgG immunoglobulin (auto-antibodies) subsets such as IgG, IgA, and IgM, complex with normal IgG and form antibody-antibody complexes, also known as rheumatoid factors (RF). Second, the target specific auto-antibodies, such as anti-collagen antibodies, complex with collagen at the joints and initiate inflammation. These two pathways initiate the autoinflammatory responses via Fc receptors and the complement cascade [5, 6]. Though the molecular mechanisms of auto-antibody production are not yet clear, studies suggest that the post-translational modifications such as citrullination and carbamylation of self-proteins could be one of the major pathways [7, 8]. These pathways lead to the generation of two unrelated and unconventional amino acids in proteins, citrulline and homocitrulline, respectively. Poor clearance leads to these altered proteins to elicit adverse immune responses. Antigen presenting cells (APCs) recognize these altered proteins and present the altered self-antigens to T cells through MHC molecules. This causes the loss of self-tolerance or immunological tissue homeostasis, consequently resulting in clonal expansion of self-antigen reactive T cells [9–11].

Recent studies have shown that Th17 autoreactive T cells, and their signature cytokine IL-17, plays a major role during the development of RA [12]. Several studies have shown that pro-inflammatory cytokines and non-cytokine inflammatory mediators contribute towards the development of Th17 cells [13]. However, the molecular mechanism of IL-23, a key cytokine, and non-cytokine inflammatory mediator such as prostaglandin E2 (PGE2), in development and perpetuation of effector Th17 cells is poorly understood. Hence in this review recent findings that provide insight regarding contribution of PGE2 and IL-23 during differentiation of pathogenic Th 17 cells have been highlighted. We have also discussed the key transcriptional factors required for Th17 development and therapeutic strategies to disrupt the interaction between IL-23 and IL-17 to prevent the end-organ damage in RA.

Possible mechanisms of IL-23/IL-17-mediated tissue destruction during RA

It has been shown that the inflammatory mediators released by the recruited major innate immune inflammatory cells, such as neutrophils and macrophages, are implicated in sustaining inflammation during RA [11]. Among these, a series of interleukins (IL-6, IL-23, IL-12, IL-1 β) and other inflammatory factors (TNF- α , CCL2, and the macrophage inflammatory protein 1 alpha, CCL3) are central to the development of RA [14]. Apart from innate immune cells, T cells are known to be the major pro-inflammatory cells recruited into the synovium. Th17 cells are newly identified lineage of T helper cells, challenging the Th1-Th2 paradigm, and are associated with IL-17 producing effector T cells that are essential for autoimmune inflammation [15]. The discovery of the key Th17 cells effector molecule, IL-17, has augmented the immune inflammatory functional aspect of other major cytokines (e.g. IFN- γ , TNF- α , IL-1 β and IL-6) and T-cell helper subsets (Th1 and Th2) [15]. Synovial cells from RA patients were later shown to produce functional IL-17 in T-cell rich areas of the synovium *ex vivo* [16]. In addition, Leipe et al [17] reported the selective infiltration of Th17 cells in the synovial microenvironment and concomitant localized expression of IL-17, strongly correlated with systemic disease activity in human autoimmune RA at both onset and progression. Furthermore, pathogenic Th17 cells that concomitantly produce IL-17 has been shown to aggravate matrix degradation in mouse model of collagen-induced arthritis (CIA) while simultaneously accelerating and enhancing the severity of synovial inflammation along with increased bone erosion [18]. The mechanism of aggravated IL-17 mediated bone erosion in CIA model could be because of the IL-17 induced upregulation of proinflammatory cytokines such as IL-6, TNF- α , IL-1 β and receptor activator of nuclear factor kappa- β ligand (RANKL) during CIA [19]. These cytokines are known to promote bone erosion and matrix degradation [19]. In support of this, pharmacological inhibition of IL-17 production reduced severe end organ damage during CIA [16]. Further, Th17 cells also secrete the receptor activator of nuclear factor kappa-B ligand (RANKL), and promotes the bone destruction phase of autoimmune arthritis by activating bone resorption cells, known as osteoclasts [20]. IL-17 also enhances collagen degradation and blocks collagen synthesis and bone formation by interfering with bone forming cells, referred to as osteoblasts [21]. The bone resorption activity of IL-17 was successfully demonstrated by blocking endogenous IL-17 with a soluble IL-17 receptor fusion protein during arthritis development [21].

In addition to the above-mentioned pathogenic cytokines, the contribution of non-cytokine immune regulators such as PGE2 towards the promotion of the inflammatory microenvironment has been well documented, as PGE2 is abundantly present in the arthritic joints [22]. PGE2 enhances the production of IL-23 and IL-1 β from innate immune cells such as macrophages and dendritic cells [22, 23]. Recent studies have shown that PGE2 directly promotes Th17 development and the secretion of its effector cytokine (IL-17) [13]. PGE2 is released by multiple immune cells in response to the activation of COX enzymes and PGE2 synthase. Studies also showed that PGE2 increases IL-17 production in presence of IL-23 and IL-1 β [24, 25]. PGE2 known to suppress both Th1 and Th2 antigen-specific human and murine T cell responses but promote Th17 cell function and differentiation

through a cyclic-AMP (cAMP) mediated EP2/EP4 receptor pathway [25]. In addition, bone restorative activity by osteoclasts was also enhanced by PGE2 [26].

In spite of the developments in Th17 subset biology, the mechanisms involved in the differentiation of naïve CD4⁺ T helper cells to pathogenic Th17 subsets are not clearly understood. However, recent studies have shown that Th17 cells are induced by the combination of non-cytokine molecules such as PGE2 along with IL-6, IL-1 β and TGF- β . Then the IL-12 (p35/p40) family member IL-23 (p19/p40) cytokine drives the perpetuation of Th17 cells through distinct mechanisms other than those that induce the development of Th1 cells and Th2 cells [27]. The possible mechanisms of PGE2 and IL-23 driven Th17 cells development are discussed below.

PGE2 and IL-23, are key regulators in Th17 development

Several reports suggest that IL-21 and IL-6 are responsible for promoting Th17 differentiation under various inflammatory conditions; however, neither of them are required for *in vivo* expansion of Th17 cells [28–30]. Recent findings support the role of IL-6 and transforming growth factor- β (TGF- β) in effectively promoting IL-17 secreting cells [31, 30]. In contrast, a high concentration of TGF- β seems to inhibit Th17 differentiation, likely through the downregulation of IL-23 receptor (IL23R) expression [32]. In addition, Th17 cells were observed in the gut of mice deficient in TGF- β receptor [33]. Importantly, *in vivo* studies have proven the essential role of IL-23 in Th17 cells and autoimmune development [34]. Conflictingly, IL-23 alone does not induce the differentiation of naïve CD4 T cells to Th17 subsets *in vitro*, but requires the combination of both IL-6 and TGF- β [35]. Although these studies suggest that IL-23 is required only for the maintenance of the Th17 phenotype and not for differentiation of Th17 cells [36], both clinical and gene deficiency data suggests that IL-23, the pro-inflammatory, heterotrimeric, co-stimulatory cytokine of Th17 cells, is essential during the development of pathogenic Th17 cells [27, 34].

In addition, recent studies revealed the importance of non-cytokine immune modulators such as PGE2 during the differentiation of naïve CD4⁺ T cells into pathogenic Th17 cells [13, 22, 37, 38]. Boniface et al [13] have shown that PGE2 signals through EP2 and EP4 receptors through cAMP pathway to promote differentiation of human and mouse naïve CD4⁺ T cells into Th17 cells and PGE2 upregulated expression of IL-23R and IL-1 β R. Moreover, PGE2 inhibited IFN- γ secretion through EP2 and upregulated IL-10 production via the EP4 receptor. These results suggest that PGE2 inhibits the Th1 differentiation and promotes the naïve CD4 T cells towards proinflammatory Th17 phenotype. Further, Boniface et al [13] demonstrated that PGE2 alone may not be able to induce the differentiation of Th17 cells and requires the combination of IL-6, TGF- β , IL-1 β and IL-23 for highest expression of IL-17.

Additionally, activated Th17 cells contribute towards bone deformities by enhancing osteoclastogenesis through the overexpression of RANKL. Among all T cell subsets, Th17 is the major contributor of RANKL. The production of IL-17, a pro-osteolytic cytokine, and RANKL together, contribute to the major outcomes of RA pathology [39]. In support of this, neutralization of IL-23, using specific neutralizing monoclonal antibodies (mAbs),

attenuated CIA in rodent models [40]. Furthermore, several reports including our recent findings (unpublished data) suggests that PGE2 enhances the osteoclast maturation from its precursor cells. These studies suggest both PGE2 and IL-23 are the potential key regulators in Th17 cells, and a drug target to prevent/attenuate inflammation as well as excessive bone degradation in RA.

These studies suggest that, PGE2 produced during the autoimmune arthritic condition plays an essential role in inducing the expression of IL-23R in naïve CD4⁺ T cells, then IL-23 released from APCs, binds to IL-23R and initiates the activation of signal transducer and activator of transcription factor 3 (STAT3). Activated STAT3 translocates to the nucleus and initiates RoR γ expression. Then activated STAT3 and retinoid-related orphan receptor gamma (RoR γ) complexes and binds to IL-17 promoter region to initiate the IL-17 production.

IL-23-mediated STAT3 and RoR γ activation are pre-requisites for Th17 development

RoR γ is the important cellular factor that coordinate the IL-17/IL-23 axis in the survival and maintenance of Th17 cells [32]. IL-23 activates STAT3 through its receptor mediated phosphorylation. Upon activation, STAT3 undergoes oligomerization and binds to the RoR γ 's promoter region, upregulating RoR γ expression. Both, STAT3 and RoR γ complex to bind to IL-17's gene promoter site to initiate Th17 cell maturation and IL-17 secretion. STAT3 also induces an anti-apoptotic signal for the survival of Th17 cells [41–43]. The orphan receptor, RoR γ , and STAT3, in turn upregulates IL-17 secretion and IL-23R expression as well as Th17 maturation and survival [44, 45]. In conclusion, the IL-23 regulated RoR γ -STAT3 pathway is critical in Th17 cell lineage maturation and maintenance at the site of inflammation during RA pathogenesis, and aggravated cartilage/bone damage.

Taken together, we have consolidated the possible mechanism of Th17 development in Figure 1. Our hypothetical model suggests that, PGE2 activates EP2 and EP4 receptors leading to cAMP production. cAMP along with other cytokines initiates the expression of IL-23R via EP2 receptor. EP4 receptors inhibits the secretion IFN- γ and upregulates IL-10 production leading to inhibition of Th1 and Th2 development respectively. Then, IL-23 secreted from APCs binds to IL-23R expressed on developing Th17 cells. IL-23-induced dimerization of activated STAT3 translocates to the nucleus and binds to RoR γ 's promoter region leading to the expression of RoR γ . Activated STAT3 binds to the RoR γ , then forming a complex on the IL-17 promoter site to induce Th17 maturation and IL-17 secretion.

Synergistic orchestra of IL-23, TNF- α , IL-1 β , IL-6, IL-12 and TGF- β during autoimmune arthritis

Although IL-23 plays a key role during the induction of Th17-mediated inflammation, the role of other pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, IL-12 and TGF- β

cannot be ignored. The synergistic and coordinated roles of these cytokines are discussed below.

The production of IL-23 from activated APCs has been demonstrated to neutralize the action of IFN- γ (Th1) and IL-4 (Th2) to favor the differentiation of Th17 cells [46]. Recent reports suggest that at the onset of inflammation, inflammatory cells secrete cytokines such as TGF- β and IL-6, inducing the expression of the IL-23 receptor on memory T cells, natural killer T cells, naïve T cells, macrophages and dendritic cells (DCs) [47]. In parallel, activated macrophages and DCs secrete IL-23, which promotes the expansion of Th17 cells [48]. The low concentration of TGF- β , secreted by regulatory T cells (Tregs), promotes Th17 cell differentiation in the presence of IL-6 [49]. Concurrently, IL-17 induces pro-inflammatory IL-1 β , TNF- α , IL-6, and IL-23 through activated synovial fibroblasts, monocytes, and macrophages which sustain inflammation and Th17 cell development [50]. Additionally, secreted IL-23 acts on APCs through its receptors, and induces pro-inflammatory cytokines IL-1 β and TNF- α along with IL-23 itself, suggesting a critical autocrine loop of IL-23 [51].

The molecular orchestra of IL-23, IL-17 and other pro-inflammatory cytokines driving bone erosion during RA is schematically illustrated in Figure 2. Our model suggests that the innate immune cells such as neutrophils, macrophages and DCs recognize the autoantibody coated or the immune-complexes (ICs) deposited at the joints. The activated cells, upon IC recognition, release a series of cytokines along with PGE2. These cytokine and non-cytokines modulators are responsible for the differentiation of Th17 cells. IL-17 secreted by Th17 cells further helps to recruit immune cells and triggers the release of pro-inflammatory cytokines and the activation of fibroblasts. In addition, Th17 cells and activated fibroblasts produce RANKL. PGE2 and RANKL promotes osteoclast formation and maturation, resulting in osteoclastogenesis and ultimately, bone erosion.

Emerging therapeutic strategies to attenuate/prevent inflammation and bone erosion during RA

The initiation of inflammation at the synovial joints occurs through the activation of immune cells that lead to the secretion of the aforementioned pathogenic cytokines, responsible for end-organ damage. Therefore, controlling the inflammation is key to prevent or attenuate the end-organ damage. Hence, several drugs have been developed and/or are being developed to inhibit the inflammation mediated by activated immune cells. Standard anti-inflammatory therapeutics may not be effective for many patients [52]. This has led to the recent development of potent immunomodulatory drugs for RA including TNF- α antagonists, T-cell co-stimulatory inhibitors, and B-cell depleting antibodies [53–56]. However, the most readily available anti-inflammatory or biological therapies are associated with several disadvantages. For instance, the continuous use of corticosteroids exacerbates RA-induced systemic skeletal damage [57]. Disease modifying anti-rheumatic drugs/biological therapies such as methotrexate, abatacept (CTLA4-Ig), rituximab (CD20+ B-cell depleting mAbs), TNF- α antagonists (infliximab and etanercept) induce severe immunosuppression, predisposing patients to serious infections and certain cancers [58, 59]. Therefore, the need

to develop new targeted therapeutic agents to effectively prevent or reduce the pathogenesis of RA is urgent.

The knowledge gained on IL-23/IL-17 through clinical and experimental studies makes it possible to develop advanced mAb therapies to target IL-17. Recent studies suggest that IL-23 is the dominant cytokine in several Th17 cell mediated autoimmune disorders such as RA, inflammatory bowel disease, and psoriasis. Several drugs were therefore developed to neutralize the pathogenic activity of IL-23. Ustekinumab is a fully humanized monoclonal antibody (hmAb), approved in 2013 for the treatment of psoriatic arthritis, and functions by binding to the P40 subunit of IL-23 and IL-12, preventing binding to its receptor IL-12 β 1 [60]. Briakinumab is a human recombinant protein selected through phage display library, lacking any immune response. It is targeted to the p40 unit of IL-12 and IL-23, reported to inhibit the interaction of these interleukins with T cells and NK cells, and proven to be effective for the treatment of autoimmune psoriasis, but retracted from the market due to its severe cardiotoxicity [61, 60, 62]. Several drugs were developed to target p19 to avoid target IL-12 simultaneously. MP-196, a mAb, selectively binds to the p19 subunit of IL-23 to attenuate RA and Crohn's diseases [61]. In addition, a fully humanized talidrakizumab (MK-3222) and guselkumab (CNTO-1959) are IL-23 antagonists, unique to the p19 unit, and are being used for treatment of autoimmune psoriasis and Crohn's disease. BI-655066 is a high affinity mAb for p19 under development for the treatment of psoriasis and Crohn's disease [60]. In addition to mAbs and several recombinant fusion proteins (Adnectin) protein antagonists have been developed to target IL-23 for various autoimmune disorders. Furthermore, several small molecular weight IL-23 antagonists were designed to inhibit Th17 development and are under investigation at the preclinical level for the treatment of certain autoinflammatory disorders [60].

Although it is logical to develop drugs that target IL-23 to attenuate or prevent the progression of pathogenic Th17 cell-mediated autoinflammatory pathologies, several drugs were developed and are used to directly target Th17 cells and its pathogenic cytokine, IL-17. Secukinumab and Ixekizumab are high affinity and selective hmAbs targeting IL-17A, neutralizing its pathogenic activity, and are approved to treat RA and other autoinflammatory disorders [60]. Brodalumab is a unique hmAb that targets the IL-17 receptor A (IL-17RA), and blocks several members of the IL-17 family cytokines, binding to IL-17RA [60].

The list of IL-23 and IL-17 drugs currently in clinical trials are tabulated in Table 1. However, the long-term safety of these drugs needs to be monitored. Further investigation of the signaling mechanisms of the IL-23/IL-17 axis in inflammatory diseases will enhance scientific insights into its immunomodulatory mechanisms to design novel targeted therapeutics.

Conclusions

Recent progress in dissecting the factors and the mechanisms that promote autoimmune arthritis pathology has suggested the critical role played by the synovial Th17 cell lineage. The key cytokine, IL-23 and non-cytokine molecules such as PGE2, are required to induce

development and maintenance of these cell lineages, and finally the secretion of IL-17 to promote bone resorption and cartilage destruction through enhanced osteoclastogenesis in RA. The coordinated role of inflammatory cytokines and non-cytokine molecules that trigger the expansion of Th17 cells and their differentiation, maturation, and perpetuation has yet to be fully resolved. Differentiation, adaptation, stability, perpetuation and function of Th17 lineage in the synovial micro-environment is critical in promoting sustained inflammation and bone erosion. Understanding these complexities in the synovial micro-environment would yield novel insights to design new targeted therapeutic strategies to control inflammation as well as end-organ damage.

Acknowledgments

We thank the late Dr. Ramprasad VR Mula for his critical comments and insights to the article.

Funding support: This work was supported by Chief Scientific officer funding for MS-Biomedical thesis from PCOM, American Heart Association award [11SDG5710004] and National Institute of Allergy and Infectious Diseases [1R03 AI128254-01A1] to R.S.

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Fig. 1. Hypothetical model of cytokine and non-cytokine mediators during the development of pathogenic Th17 CD4⁺ T cells

PGE2 induces cAMP leading to the expression of IL-23R along with pro-inflammatory cytokines in naïve CD4⁺ T cells. Upon binding of IL-23 to IL-23R, activated dimers of STAT3 translocate to the nucleus and activates RoR γ promoter region. Then the activated STAT3 binds to RoR γ forming a complex on the IL-17 promoter site to induce Th17 maturation and IL-17 secretion.

Fig. 2. Schematic representation of the synergistic function of cytokines and non-cytokine molecules in bone erosion during RA

Innate immune cells activated by ICs secrete several pro-inflammatory cytokines and non-cytokine molecules such as PGE2. These pro-inflammatory molecules initiate the differentiation of naïve CD4⁺ T cells to pathogenic Th17 CD4⁺ T cells. Then Th17 cells secrete IL-17, which activates immune cells and fibroblasts. Activated Th17 and fibroblast cells secrete RANKL. Both PGE2 and RANKL promote osteoclast maturation resulting in bone erosion.

Table 1

A summary of the drugs targeting IL-23 and IL-17 to attenuate the inflammation during autoinflammatory disorders.

Drug	Drug Class	Target	Mechanism
Ustekinumab	Humanized Monoclonal Antibody	p40 subunit of IL-23/ IL-12	Prevents binding to its receptor IL-12 β 1 therefore blocking subsequent signaling [52].
Briakinumab	Humanized Monoclonal Antibody	p40 subunit of IL-12/ IL-23	Inhibits T cells and NK cells and proven to be effective for autoimmune psoriasis [52].
MP-196	Monoclonal Antibody	p19 subunit of IL-23	Treats RA and Crohn's diseases via blockade of the p19 subunit of IL-23 [52].
Tildrakizumab	IL-23 antagonist	p19 subunit of IL-23	Treats autoimmune psoriasis and Crohn's disease [54].
Guselkumab	IL-23 antagonist	p19 subunit of IL-23	Treats autoimmune psoriasis by neutralizing IL-23 [55]
BI-655066	High affinity Monoclonal Antibody	p19 subunit of IL-23	Treats psoriasis and Crohn's disease by binding to IL-23A with high affinity therefore blocking the biological activities of IL-23 [51, 56].
Adnectin	Fusion Protein	IL-23	Attenuates autoimmune disorders [57].
Secukinumab	High Affinity and Selective, Human IgG1 κ Monoclonal Antibody	IL-17 receptor A	Neutralizes the pathogenic activity of IL-17A [58].
Ixekizumab	High Affinity and Selective, Human Monoclonal Antibody	IL-17 receptor A	Neutralizes the pathogenic activity of IL-17A [59].
Brodalumab	Humanized Monoclonal Antibody	IL-17 receptor A	Blocks many of the members of the IL-17 family cytokines binding to its IL-17RA [60].
Tocilizumab	Humanized Monoclonal Antibody	IL-6 receptor	Inhibits IL-6-mediated pro-inflammatory signaling. Restores homeostatic balance between Th17 cells and Treg cells in patients with RA [61].