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Review

Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies

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ABSTRACT

Interleukin 17 (IL-17) is a proinflammatory cytokine that has been the focus of intensive research because of its crucial role in the pathogenesis of different diseases across many medical specialties. In this context, the present review in which a panel of 13 experts in immunology, dermatology, rheumatology, neurology, hematology, infectious diseases, hepatology, cardiology, ophthalmology and oncology have been involved, puts in common the mechanisms through which IL-17 is considered a molecular target for the development of novel biological therapies in these different fields. A comprehensive review of the literature and analysis of the most outstanding evidence have provided the basis for discussing the most relevant data related to IL-17A blocking agents for the treatment of different disorders, such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, cardiovascular disorders, non alcoholic fatty liver disease, multiple sclerosis, inflammatory bowel disease, uveitis, hematological and solid cancer. Current controversies are presented giving an opening line for future research.

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1. Introduction

The IL-17 family of cytokines consists of 6 proteins (IL-17A to IL-17F) and 5 receptors (IL-17RA to IL-17RE) which are structurally unrelated to any other known cytokine receptor (Fig. 1) [1]. IL-17A and IL-17F are produced by several types of immune cells, while IL-17B, IL-17C and IL-17D are mostly produced by epithelial cells. IL-17 receptors are widely distributed across common cell types at different tissues.

Depending on the nature of the responder cell, the ligation of IL-17R initiates signaling pathways leading to activation of the transcription factors NFκB, IκBζ, AP1 and C-EBP, which induce transcription of several genes in a tissue-specific fashion [3]. Among the most relevant, inflammatory cytokines (TNF, IL-6, IL1β, G-CSF, GM-CSF), chemokines (IL8, CXCL1, CXCL2, CXCL5, CCL2, CCL7, CCL20), matrix metalloproteinases (MMP1, MMP3, MMP9, MMP12, and MMP13), and also different proteins to preserve epithelial barrier function such as bactericidal peptides (cathelicidins, α and β defensins), claudins and mucines [4] (Table 1).

Despite its proinflammatory effect, IL-17A and IL-17F alone are not powerful inflammatory cytokines. In fact, its potent inflammatory action is mostly related with its capability to recruit immune cells, and with its synergistic actions with other proinflammatory cytokines such as TNF, IL-1β, IFNγ, GM-CSF, IL-22 [5]. By recruiting and activating neutrophils, and at lesser extent monocytes, IL-17A and IL-17F cytokines are central players in the physiological immune response against extracellular bacteria and fungi. Its protective function is mostly relevant at mucosal surfaces and skin where, upon appropriate stimuli, IL-17 cytokines are immediately released and contribute to epithelial homeostasis, to inflammatory acute responses and B cell stimulation [6], thus acting as a bridge between innate and acquired immune responses.

IL-17A is the hallmark of the Th17 subset of CD4 lymphocytes, which also produce IL-17F, IL-22 and IL-21. Th17 differentiation is dependent on the presence of proinflammatory IL-6 and IL-1β, but surprisingly also TGFβ, an anti-inflammatory cytokine produced by several non-immune cells. Th17 differentiation requires simultaneous activation of the transcription factors STAT3 (IL-6 dependent) and ROR-c (TGFβ-dependent). After differentiation, Th17 express IL-23-R and require IL-23 for proliferation and survival. However, it is now recognized that IL-17 is also produced by CD8 lymphocytes and by tissue-resident innate cells such as NK, NKT, Tγδ, and ILC3 lymphocytes, which are rapidly activated after injury or infection to secrete IL-17 in an HLA-independent fashion. In fact, from an evolutionary perspective, IL-17 is an ancient cytokine already identified in lampreys with little evolutionary variation over 360 million years and therefore lacking an adaptive immune system [7]. Production of IL-17A by myeloid cells (neutrophils, mastocytes) is controversial due to its capability for extracellular environmental IL-17A endocytosis [8]. Whether IL-17 production by the different types of innate immune cells is strictly IL-23-dependent is a matter of intensive debate [9–11]. In this sense, it has been shown that in persistent psoriatic manifestations and psoriatic arthritis, innate immune cells can be a non-IL-23 dependent source of IL-17A, which can contribute to the pathogenesis of these diseases [12].

In the same way that monogenic defects in the IL-17 pathway – as observed in Hyper-IgE syndrome, chronic muco-cutaneous candidiasis and APECED syndrome – are associated with increased susceptibility to infections mainly by *Candida sp.* and *Staphylococcus aureus* [13], unrestrained IL-17 production has been demonstrated to be involved in the pathogenesis of several chronic inflammatory disorders, as well as organ-specific autoimmune diseases. Notwithstanding basic intensive research, several gaps in the knowledge of the pathogenic role of IL-17 cytokines exist. Among them, two important uncertainties have already emerged. First at all, the relevance of distinctive IL-17-producing cells and how they are locally activated in different pathologies is just beginning to be explored. For instance, ILC3 seems to be the key IL 17-producing cell at the enthesis in SpA [14], while tissue-resident memory CD8 T constitute the majority of intradermal T cells in psoriatic plaques [15]. Secondly, the role of Th17 cells in human diseases is difficult to establish because they do not display a terminal differentiation phenotype, but characteristically exhibit instability, plasticity, and functional heterogeneity, including pathogenic and non-pathogenic phenotypes. The distinctive features of the various Th CD4 effector/regulatory subpopulations are determined largely by the set of lineage-specific transcription factors they express and the cytokine genes they transcribe. The induction of the distinctive patterns of gene expression is dependent on the local cytokine milieu during the antigen-presenting cell mediated activation of a naïve T cell (Th0) (Fig. 2). Moreover, tisular factors such as dysbiosis, pH modifications or dietary intakes, by exerting epigenetic changes, can further promote transitory changes in Th differentiation programs [16]. Thus, Th17 cells expressing their

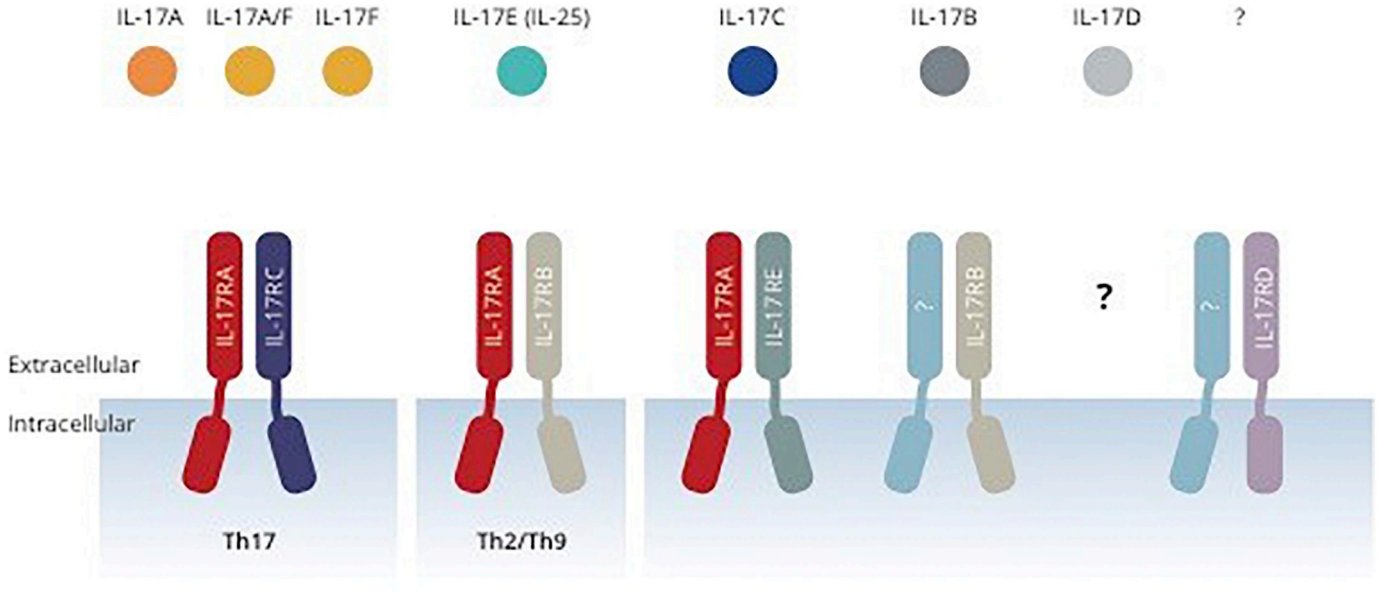

Fig. 1. IL-17 Cytokine and receptor families [2].Note added in proof: it has recently been identified that IL17RB also uses ILRA chain for signal transduction of type 2 cytokines[184].

Table 1
IL-17 functions in homeostatic conditions.

Molecule	Actions
IL-17 A IL-17 F	– Stimulate the production of neutrophils – Potent chemotactic effect on neutrophils (and monocytes) – Production of mucus – Production of antimicrobial peptides – Epithelial integrity with secretion of claudins – Production of inflammatory chemokines/cytokines

signature transcription factor ROR-c and secreting IL-17A can simultaneously co-express Tbet and secrete also IFN-γ (dual Th lymphocytes) (Fig. 2). Moreover the pro-inflammatory ROR-c Th17 cell producing IL17 can simultaneously transcribe Fox-P3 and thus achieve the capability to co-produce IL10, an anti-inflammatory cytokine (15). In healthy individuals, the majority of Th17 cells are nonpathogenic and found at mucosal sites where they promote tissue repair and contribute maintain barrier functions. It would therefore make sense that the default Th17 differentiation program would favor a nonpathogenic phenotype that could be converted into a pathogenic phenotype in presence of additional proinflammatory signals, such as IL-1β or IL-23 [17].

Targeted manipulation of the immune system in animal models has led to insights into disease pathogenesis, but is contribution to formulate clinical and therapeutic concepts in humans has been much more limited [18]. Thus, in experimental animal models of chronic inflammatory diseases such as posterior uveitis, psoriasis, inflammatory bowel disease, multiple sclerosis, collagen-induced arthritis and ankylosing spondylitis, IL-17A appeared to be a crucial pathogenic molecule. However, results of clinical trials with anti-IL-17 antibodies in Crohn disease, RA and refractory posterior uveitis have been discouraging or only partially effective in spite of strong evidence for a dominant pathogenic role of IL-17A in Crohn [19,20], RA [21] and posterior uveitis [22,23] (Table 2). On the other hand, IL23/IL17 blockade is highly effective in Psoriasis, Ankylosing Spondylitis and Psoriatic arthritis, and therefore a few monoclonal antibodies selectively acting at different points of the IL23/IL17 axis are currently approved and marketed (Fig. 3).

2. Dermatology

2.1. Psoriasis

The central role of IL-23/Th17 axis in the pathogenesis of psoriasis has been the focus of extensive research. Selective antagonists to IL-23, IL-17, IL-22, IFNγ, and IFNα have been examined as therapeutic targets. Although several isoforms of IL-17 have been identified, IL-17A is the best characterized from a functional and pathogenic perspective. Blockade of IL-17A (ixekizumab and secukinumab), the IL-17 receptor A subunit (brodalumab) or IL-23p19 (guselkumab, risankizumab, tildrakizumab, mirikizumab) can reverse clinical, histologic, and molecular features of psoriasis. In contrast, IL-22 and IFN-γ have a smaller pathogenic role, given that single antagonism of these cytokines with neutralizing antibodies has not been associated with marked clinical improvement, highlighting the predominant pathogenic role of the IL-23/IL-17 axis in patients with psoriasis [31].

Blocking IL-17A with targeted treatments might be more far-reaching than previously thought, and evidence is accumulating that cells of the innate immune system, like neutrophils, mast cells, γδ T cells and innate lymphoid cells (ILC3) might also be an important source of IL-17A in psoriasis [32]. Relevant finding is the presence of cells other than T lymphocytes (most likely innate immune cells) expressing IL-17A independently from IL-23 in psoriatic plaques refractory to ustekinumab therapy [33].

However, activated monocytes and T lymphocytes have been suggested to be the dominant source of IL-17A rather than neutrophils [34]. Moreover, it has also been demonstrated that clinically resolved psoriatic plaques contain psoriasis-specific IL17-producing long-lasting resident memory T CD4 and T CD8 clones [35].

Recent studies have provided interesting clinical data on drugs targeting the IL-17-Th17 pathway. In a head-to-head, double-blind study, secukinumab demonstrated sustained superior efficacy than ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis through week 52, with greater reductions in psoriasis-related pain, itching, and scaling, and greater improvement across all quality-of-life measures evaluated, with a favorable safety profile [36]. Also, treatment with secukinumab 300 mg at a fixed-interval schedule (every 4 weeks) has demonstrated sustained efficacy in achieving ≥ 90%

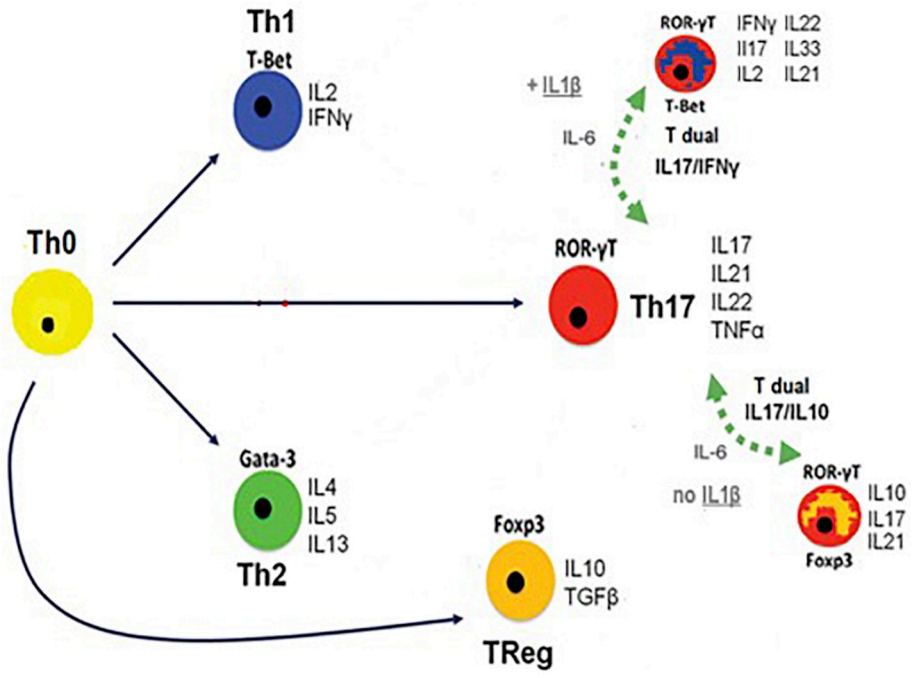

Fig. 2. Th differentiation patterns. After antigen processing, dendritic cells are activated and start secreting specific cytokines and present antigen peptides in a HLA-dependent fashion to Th0 naïve cells. According to the factors present at the immunological synapse, Th0 initiate a program of lineage-specific transcription factor (TF) expression which allows for transcription of genes characteristic of each Th differentiation pathway: Tbet = Th1; Gata-3 = Th2; ROR-γT (ROR-c) = Th17; Fox-P3 = Treg. However, depending on the local tisular and cytokine milieu, simultaneous transcription of more than a TF is possible, allowing for more than one lineage-specific cytokine production ("Dual" Th cells). This possibility may render a Th17 cell pathogenic or not pathogenic.

Table 2
Clinical efficacy of IL-12/IL-23 pathway modulators [24–26].

Diseases	IL-12 + IL-23 (p40) (Ustekinumab)	IL-23 (p19) (Guselkumab, Tildrakizumab, Risankizumab, Mirikizumab[a])	IL-17A (Secukinumab, Ixekizumab)	IL-17RA (Brodalumab)	IL-17A-F (Bimekizumab[a])
Psoriasis	Approved	Approved[b]	Approved	Approved	Not approved (phase 3 ongoing)
Psoriatic arthritis	Approved	Not approved (phase 3 ongoing)	Approved	Not approved (phase 3 completed)	Not approved (phase 3 ongoing)
Ankylosing spondylitis	Not approved (phase 2 endpoint not met for risankizumab)	Not approved (phase 2 endpoint not met for risankizumab)	Approved[c]	Not approved (phase 2 withdrawn)	Not approved (phase 3 ongoing)
Non-radiographic Axial Spondyloarthritis	Not approved (phase 3 endpoint not met)	Not approved (phase 3 ongoing)	Not approved (phase 3 ongoing)	Not tested	Not approved (phase 3 ongoing)
Asthma	Not tested	Not tested	Not tested	Not approved (phase 2 withdrawn)	Not tested
Crohn's disease	Approved	Not approved (phase 3 ongoing)	Not approved (phase 2 endpoint not met)	Not approved (phase 2 withdrawn)	Not tested
Multiple sclerosis	Not approved (phase 2 endpoint not met)	Not tested	Not approved (phase 2 endpoint not met)	Not tested	Not tested
Rheumatoid arthritis	Not approved (phase 2 endpoint not met)	Not approved (phase 2 endpoint not met)	Not approved (phase 3 completed)	Not approved (phase 2 withdrawn)	Not approved (phase 2 completed)
Uveitis (non-infectious)	Not tested	Not tested	Not approved (phase 2 completed)	Not tested	Not tested

[a] Phase 3.
[b] Mirikizumab is not currently approved for this indication.
[c] Ixekizumab is not currently approved for this indication.

improvement in Psoriasis Area and Severity Index (PASI 90) and in overall and subscale scores on all quality-of-life instruments, which has been maintained through 5 years with no new safety concerns [37]. Furthermore, three phase III trials have shown that ixekizumab, a monoclonal antibody against interleukin-17A, was superior to placebo and etanercept in the treatment of moderate-to-severe psoriasis through 60 weeks of treatment [38].

Data from three prospective phase III studies of secukinumab with a follow-up of 2.5 years demonstrated long-lasting efficacy and safety in the complete spectrum of psoriasis manifestations, including palmoplantar, nail, and scalp manifestations [39]. In moderate-to-severe genital psoriasis with ≥ 1% body surface area involved, ixekizumab has been shown to be superior to placebo at week 12 [40].

Aiming to understand the potential of IL-17 inhibitor secukinumab for disease modification and based on the fact that a portion of patients did not relapse for at least 1 or 2 years post-discontinuation of secukinumab therapy [41], the ongoing STEPin study investigates whether early intervention with secukinumab versus narrow-band ultraviolet B (nb-UVB) phototherapy in subjects with new-onset psoriasis can modify the long-term natural course of the disease and thus become a novel treatment strategy for patients with psoriasis [42].

To test the concept of a very early intervention in PsA, recent exploratory study has shown that in psoriatic patients with arthralgia and inflammatory changes in the joints very early treatment with secukinumab led to resolution of inflammation and no progression of joint bone changes after 24 weeks [43]. However, additional research is needed to further understand this approach.

2.2. Other diseases

IL-17A has also been linked to the pathogenesis of *atopic dermatitis* (AD). In experimental AD models, IL-17A was shown to be an inducer of Th2-mediated immune response [44,45] and to contribute to the damage of skin barrier proteins, with reduced expression of filaggrin and claudin 1 in lesional atopic skin; filaggrin expression and disease severity have been found to be inversely correlated [46]. Moreover, elevation of skin and serum levels of IL-17A in AD emphasizes the systemic inflammatory profile of this dermatosis. Although IL-17A may mediate AD-related immune dysregulation by amplifying the inflammatory response [47], the proposal of IL-17A as an attractive target for AD is still unclear. AD is now considered to be heterogeneous, with additional activation of Th22, Th17/IL-23, and Th1 cytokine pathways depending on the subtype of the disease, and the immune activation seems to extend beyond lesional AD, since non-lesional skin and the blood component harbor AD-specific inflammatory changes. Future therapies should probably focus on a systemic treatment approach, especially in patients with moderate-to-severe disease [48].

The precise pathogenesis of *alopecia areata* remains unknown. However, this disease seems to be triggered by helper T cell infiltration in hair follicles. Infiltration of CD4(+)IL-17A(+) Th17 cells in the dermis, particularly around hair follicles was found in patients with alopecia areata, including single patch alopecia areata, multiple patch alopecia areata, alopecia totalis and alopecia universalis [49]. These findings suggest that alopecia areata is induced by a Th17-associated autoimmune mechanism. A quantitative analysis of IL-17-producing cells in different lesional skin of several forms of alopecia areata showed that the ratio of IL-17-producing cells in acute, diffuse and total alopecia was significantly lower than in patchy alopecia areata. Regarding IL-12, IL-17, and IL-23 receptor gene polymorphisms, IL-12 and IL-23R polymorphisms did not show a significant association with alopecia areata, but the IL-17 GG genotype was associated with susceptibility to the disease, even though this phenotype was present in a small number of patients [50]. Th17 cell counts have been found to be significantly higher than those of T_{reg} in patients with alopecia areata (45). Furthermore, Th17 cell counts in patients with disease of short duration or in active phase were significantly higher than their

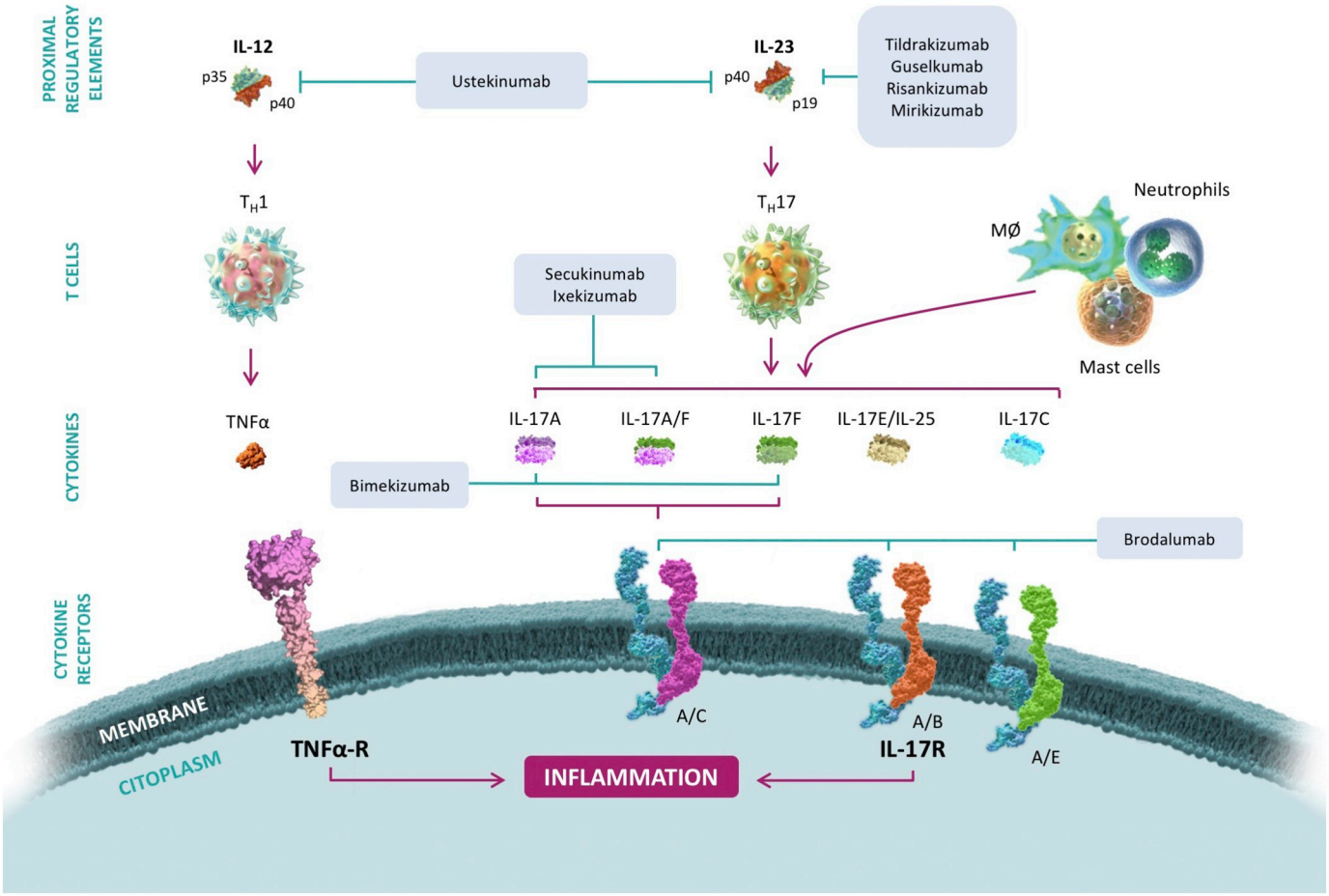

Fig. 3. Different targets and antagonists of the IL-23/IL-17 pathway already approved [27–30].

respective counterparts, both in lesional skin and in peripheral blood mononuclear cells. In another study, the expression of IL-17, IL-22, Foxp3 and B cell activating factor (BAFF), a regulator of T cell activation, was evaluated in tissue and sera of patients with alopecia areata [51].Tissue and serum levels of IL-17, and tissue levels of IL-22 and BAFF were significantly higher in patients with alopecia areata than in controls. A significant positive correlation was found between both tissue levels of IL-17 and BAFF, and tissue levels of IL-22 and disease duration. These data draw attention to the possible synergistic involvement of Th17 cells and BAFF in the pathogenesis of alopecia areata.

In tissue samples of *hidradenitis suppurativa*, IL-12 and IL-23 were found to be abundantly expressed by macrophages infiltrating papillary and reticular dermis of lesional skin. In addition, IL-17-producing T helper cells were found to distinctly infiltrate the lesional dermis, suggesting the involvement of the IL-23/Th17 pathway [52]. In a study of 86 patients with hidradenitis suppurativa and 86 matched healthy volunteers aimed to determine serum levels of IL-17 in both groups, the mean serum levels in patients were significantly higher than in healthy volunteers [53]. Also, a tendency toward higher serum IL-17 concentrations in patients with more advanced disease was observed [53].

According to current data, anti-IL-17 agents seem promising agents to treat hidradenitis suppurativa. An ongoing pilot study evaluates the safety and feasibility of secukinumab for patients with moderate-to-severe hidradenitis suppurativa, as well as informs on the effect size that will be useful for future larger randomized control trial with an active comparator (Clinical trial NCT 03099980).

2.3. Controversies

In addition to the previously described diseases, it has been recently suggested a role for IL-17 in the pathophysiology of a large number of dermatological inflammatory dermatoses, such as lichen planus, pyoderma gangrenosum, pemphigus vulgaris, pemphigoid, or dermatitis herpetiformis. The potential activity of IL17A inhibitors in the control of these diseases, as well as their long-term efficacy and safety, and their potential for psoriatic disease modification, is a challenge for the scientific community.

3. Rheumatology

The IL-23/IL-17/IL-22 cytokine axis has been shown to be involved in the pathogenesis of chronic arthritis (Fig. 4) and structural damage including bone erosion, and new bone formation in experimental models of spondyloarthritis (SpA) [54,55].

In animal models of inflammatory arthritis (collagen-induced arthritis), IL-17A gene transfer induced the expansion of IL-17RA(+)CD11b(+)Gr1(low) osteoclast precursors and a concomitant elevation of biomarkers indicative of bone resorption. This occurred at a time preceding noticeable joint inflammation, suggesting that IL-17A is critical for the induction of pathological bone resorption through direct activation of osteoclast precursors [56]. In validated animal models of SpA, blockade of IL-17A, but not of TNF-α, reduced clinical manifestations, with radioimaging and histological data showing that IL-17A blockade also impact structural damage, including pathologic new bone formation [54,57]. Also, IL-23 has been shown to be essential in the development of an experimental model of enthesitis acting on IL-

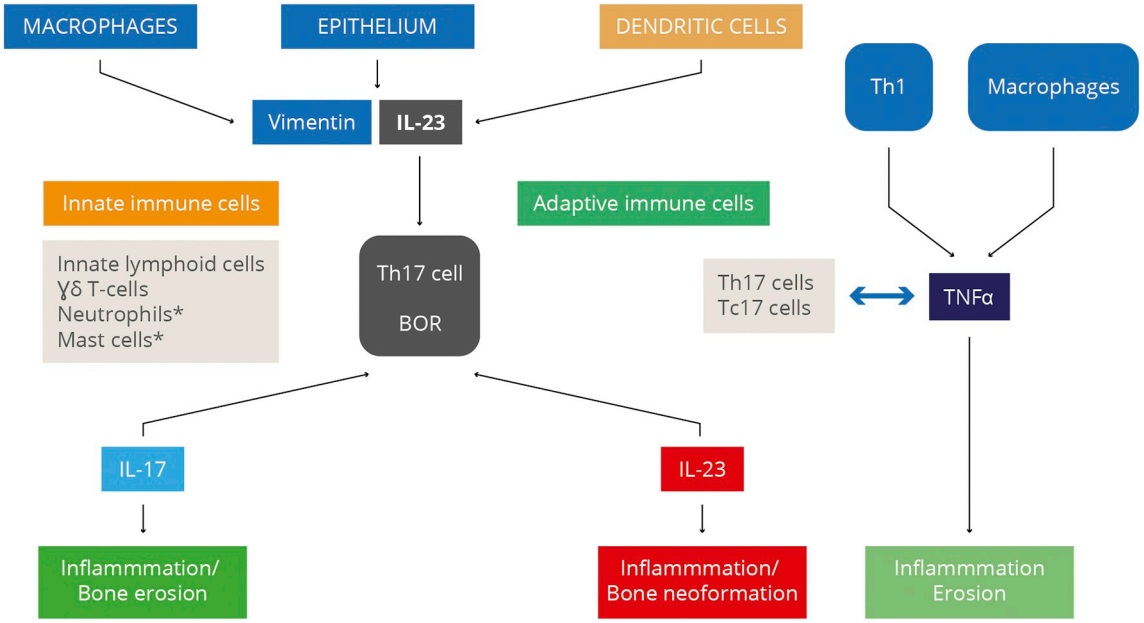

Fig. 4. The inflammatory cascade resulting in the production of IL-17 cells originates in the macrophages and dendritic cells. Several types of cells of the innate and adaptive immune systems produce IL-17 which along IL-22 is involved in bone neoformation. *There is no clear evidence of IL-23R expression; IL, interleukin; ROR, RAR-related orphan receptor; Tc, cytotoxic T cell; Th, T-helper cell; TNF, tumor necrosis factor.

23 receptor, RAR-related orphan receptor γt (ROR-γt), and stem cell antigen 1 (Sca1)(+) entheseal resident CD4-CD3-T cells [14]. Besides evidence from animal models, it has been showed the in vitro capacity of IL-17A to induce differentiation of osteoblasts from synovial biopsies of SpA patients [57]. Moreover, local, but no systemic IL-17 A, induced polarizacion of anti-inflammatory Mesenchymal stem cells type 2 (MSC2) and bone neoformation in AS patients [58].

3.1. Psoriatic arthritis

Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease belonging to the concept of spondyloarthritis which is characterized by a wide musculoskeletal (arthritis, enthesitis, spondylitis, dactylitis) and cutaneous (skin and nail psoriasis) involvement with extrarticular features such as bowel inflammatory disease and uveitis. Genetically and clinically is a very heterogeneous disease [59], and its pathophysiology, i.e, the relative expression of IL-23/IL-17 or TNF pathways, seems to be different in the distinct tissues involved [60].

In synovial tissue and fluid samples from PsA, IL-23A mRNA expression correlated with C-reactive protein levels and swollen joint count [61]. Although Th17 cells were reported as the pathogenic cells implicated in animal models of arthritis, mast cells are the main cells expressing IL-17A in synovial tissue of patients with peripheral SpA, including PsA, while very few IL-17+ T cells were found [62]. However, mast cells do not synthesize, but rather capture IL-17A from the extracellular medium and release it after an inflammatory/infectious challenge [8]. Recent evidence supports the presence of IL-17A-positive mast cells across different SpA-related target tissues (skin, gut, synovial tissue), and the inverse correlation between its IL-17A content and inflammation indicate that IL-17A in mast cells can be regulated [63]. Therefore, tissue-resident mast cells may act as IL-17A-loaded sentinel cells and release IL-17A to amplify inflammation and should therefore be further investigated to understand how IL-17A can be controlled locally during tissue inflammation [63].

Other IL-17 A producing cells may also have pathogenic relevance in PsA. IL-17A+ CD8 T cells are enriched in synovial fluid of PsA patients and correlate with disease activity, power Doppler signal and erosive disease [64]. Innate lymphocyte cells (ILC) are increased in peripheral blood of PsA patients, and distinct changes of ILC subpopulations are associated with clinical disease activity as well as imaging signs of inflammation and structural damage. In clinically active PsA, ILC3 (induced by IL-23 and synthesizing IL-17, IL-22) were significantly increased at the expense of ILC2s (synthesize IL-4, IL-5, IL-9 and IL-13), supporting the concept of IL-23/IL-17 pathway activation is also the driving force of inflammation in PsA patients [65,66].

Although IL-23 is needed to the development of Th17 and Tc17 cells as well as to induce IL-17 and IL-22 production of innate immune cells expressing the IL-23-receptor, there are many other innate immune cells producing IL-17 in an IL-23-independent manner. Depending of the predominance of the subtype of IL-17A expressing cell in the different tissues (gut, skin, musculoskeletal, etc) in PsA or AS patients, IL-23 or IL-17A targeted therapies could be or no efficacious. Studies on expression of IL-23/IL-17 cytokine axis are warranted to better define the more convenient target.

In patients with active PsA treated with secukinumab, the extension phase of the FUTURE 1 trial [67], confirms long term (156 weeks) efficacy in all endpoints, including (American College of Rheumatology) ARC20 response, quality of life, and radiographic progression [68]. ARC20/50/70 responses were sustained through 5 years of treatment [69]. On the other hand, the first RCT evaluating the efficacy of a biologic treatment in the management of axial manifestations in patients with PsA recently demonstrated rapid and significant improvement in ASAS20 response through Week 12 of secukinumab vs. placebo [70].

The PSARTROS study was designed to elucidate the effects of IL-17A inhibition on inflammation and bone changes in joints affected by PsA [71]. In this open-label study, 20 patients with PsA received 24-week treatment with secukinumab, which led to significant improvement of synovial inflammation (MRI, power Doppler ultrasound, and high-resolution peripheral quantitative computer tomography [72] of the hands), with no progression of catabolic and anabolic bone lesions.

3.2. Ankylosing spondylitis

In ankylosing spondylitis (AS), serum concentrations of IL-23 are elevated and polymorphisms in the IL-23 receptor are associated with AS and PsA. Other studies have shown increased numbers of circulating Th17 cells in the peripheral blood of patients with SpA, included AS,

which were also polyfunctional in terms of T cell receptor-driven cytokine production [73]. In addition, peripheral blood levels of Th22 and Th17 cells were reported to be elevated in patients with AS [74].

Dysbiosis is reported as the inducer of subclinical gut inflammation and production of IL-23 which actives ILC3, which are proposed to migrate to the joints where they may trigger inflammation and bone neoformation through IL-17 and IL-22 release [75].

Results from clinical trials support the efficacy and safety of agents that block IL-17 (secukinumab and ixekizumab) in AS patients [76]. In a 3-year extension study of the randomized MEASURE 1 trial [76] in 274 patients with AS, secukinumab provided sustained efficacy in signs, symptoms and physical function, without new safety signals [77]. The efficacy and safety of secukinumab has been confirmed in 80% of patients who entered in the extension study and completed 5 years of treatment [78]. In patients with AS treated with secukinumab for 2 years (weekly after 4 weeks and every 4 weeks thereafter), improvement in pain and fatigue scores were documented, which were noted in both subgroups of patients with hsCRP elevated or normal baseline values, as well as in anti-TNF-naïve patients or with TNF inadequate response [77].

Unexpectedly, neither risankizumab nor ustekinumab IL-23 antagonists, have shown efficacy in phase II study in patients with AS [25], challenging the pathogenic role attributed to IL-23 in animal models of SpA [14] and providing evidence of the distinct roles of IL-23/IL-17 axis components in the different tissues of different SpA conditions.

3.3. Rheumatoid arthritis

High levels of serum IL-17 A and increased number of Th17+ circulating cells have been reported in RA. As in PsA, in RA synovial tissue mast cells are the main IL-17A+ cells, with less proportion of IL17A+ neutrophils and very few IL17A+ T cells. Peripheral blood levels of Th22 and Th17 cells were elevated and correlated with disease activity in patients with RA [74].

In a phase 3 randomized double-blind clinical trial, the anti-IL-17A antibody, secukinumab, at a dose of 150 mg resulted in improvement in signs and symptoms and reduced disease activity in patients with active RA who had an inadequate response to TNF inhibitors [79]. However, treatment with ustekinumab (anti-IL-12/23 p40 antibody) or guselkumab (anti-IL-23 antibody) did not significantly reduce the signs and symptoms of RA [26].

The modest response of RA to secukinumab could perhaps be explained by disease heterogeneity. Interestingly, the subgroup of RA patients with synovial tissue ectopic lymphoid neogenesis (ELN) had a robust expression of IL-23 and its downstream cytokines, IL-17F, IL-22 and IL-21. This observation raises the question of whether in the group of patients with synovial ELN, targeting this pathway may specifically provide larger clinical benefits [80].

3.4. Controversies

Although IL-23 is needed for development of Th17 and Tc17 cells as well as to induce IL-17 and IL-22 production by innate immune cells expressing the IL-23-receptor, there are many other innate immune cells producing IL-17 in an IL-23-independent manner. Depending on the predominance of the subtype of IL-17A producing cell in the different tissues (gut, skin, musculoskeletal, etc) in PsA or AS patients and/or the clinical stage, IL-23 or IL-17A targeted therapies could be or no efficacious [81].

As an example, experimental models support the key pathogenic role of IL-23 in the development of enthesitis, spondylitis, bone neoformation and erosions through IL-23R + RORgt + CD3 + CD4-CD8- enthesitis-resident cells [14]. In axial tissues of AS patients, it has been demonstrated that IL-23/IL-17 producing cells are macrophage and dendritic cells expressing IL-23 and myeloid cells (neutrophils) expressing IL-17A. Despite of these findings, clinical trials confirms that only TNF and IL-17 A are effective therapeutic targets in AS [25].

4. Hepatology

Liver is one of the main producers of IL-17A [82] and IL-17RA is thoroughly expressed in liver cells as hepatocytes, sinusoidal cells, biliary cells, and stellate cells [82,83]. In mouse models, IL-17A blockade (genetic deletion or antibody neutralization) protects from liver injury [84] whereas its administration increases liver damage [85]. In humans, IL-17A has been studied in hepatitis B [86] and C [87], alcohol [88], primary biliary cholangitis [89], acute rejection in liver transplant [90], hepatocellular carcinoma [91], autoimmune hepatitis [92], and primary sclerosing cholangitis [92]. In all of them, the IL-17 axis is overexpressed and its blockade is suggested as of future therapeutic benefit [83,86–92].

Nowadays, the focus of interest is shifting to non-alcoholic fatty liver disease (NAFLD) as it has become the most important and severe liver disease leading to liver transplant [93,94]. NAFLD is characterized by excessive hepatic fat accumulation defined by the presence of steatosis in > 5% of hepatocytes [95] and is considered the hepatic manifestation of the Metabolic Syndrome [95]. Other non-related diseases to Metabolic Syndrome can provoke fatty liver, as excessive alcohol consumption, and infrequent genetic diseases [95]. A strong association is recognized in the last years between fatty liver and psoriasis so that these patients suffer a higher prevalence and severity of both when they coexist [96].

NAFLD pathogenesis is complex and multifactorial. The disease is the final result of the not yet perfectly understood interaction between lifestyle (diet, physical activity) and genetic background [96–98]. Insulin resistance is the key factor linking Metabolic Syndrome and NAFLD [99]. The liver is influenced by peripheral insulin resistance, mainly mediated by proinflammatory cytokines as TNFα, IL-6 and IL-17 [99]. But the liver is also influenced by a specific process of intrahepatic insulin resistance mediated by an excess of free fatty acids released from adipose tissue that became lipotoxic inducing accumulation of hepatic diacylglycerols and activation of inflammatory pathways that, in turn, inhibit insulin signaling and lead to hepatic insulin resistance [99]. IL-17 plays a central role in this inflammatory hepatic response [100]. There is an increase in IL-17 production driven by natural killer (NK), natural killer T (NKT), and Th17 cells. NK cells represent one third of liver lymphocytes and are the main source of liver IFNγ [100]. They have been shown to be involved in fatty liver progression [101]. NKT are also an important part of liver immunity as producers of IFNα, IFNγ, and IL-17 [102]. NKT cells modulate fibrogenic and inflammatory responses in liver tumors, autoimmune hepatitis and viral hepatitis although its role in NAFLD is yet unclear [102]. Th17 cells are the primary source of IL-17 [103]. Obesity drives increased levels of Th17 cells and IL-17 production whose levels are increased in fatty liver [104]. Increased levels of IL-17 induced by NK, NKT and Th17 cells activate IL-17AR in a subset of liver cells, mainly hepatocytes, Kuppfer cells, and hepatic stellate cells. Triglyceride-stored hepatocytes in NAFLD are more susceptible to stress damage [105]. IL-17 overexpression further increases hepatocytes lipid uptake aggravating damage and rendering hepatocytes prone to cell death and disease progression [105]. Kuppfer cells play a critical role in liver homeostasis as regulators of hepatic pathogenesis via activation of inflammation (IL-6, IL-12, TNFα) [106]. The stimulation of Kuppfer cells by IL-17 results in intense production of IL-6 and TNFα [107] and its depletion protects from liver damage [85]. IL-17- activated Kuppfer cells augment liver fibrosis [107]. Hepatic stellate cells (HSC) are the main source of extracellular liver matrix, and hyperactivation induces liver fibrosis in almost all liver disorders [108]. IL-17 induced by Th17 cells and Kuppfer cells, in turn induced by IL-17, provoke HSC collagen production [107]. The IL-17 -mediated activation of hepatocytes, Kuppfer cells, and HSC leads to further proinflammatory cytokine and

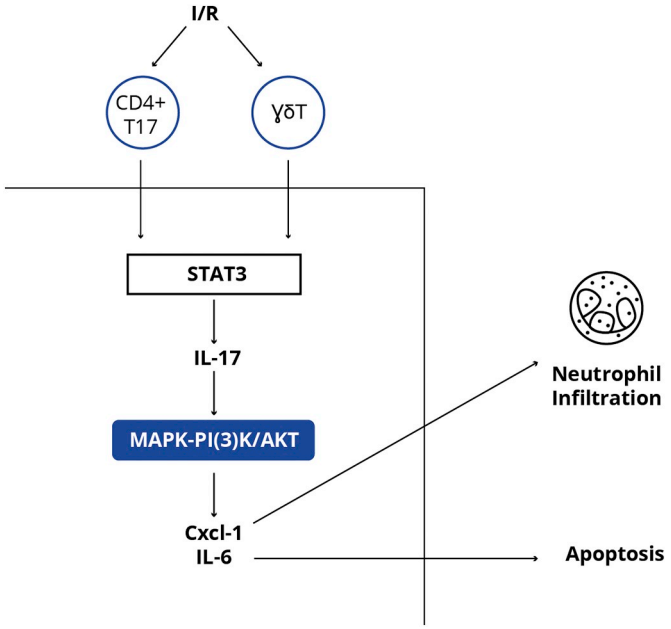

Fig. 5. Pathogenic role of IL-17 in myocardial ischemia/reperfusion injury. IL-17 is activated by signal transducer and activator of transcription 3 (STAT3), which in turn activates MAPK-PI(3)K/AKT leading to production of C-X-C chemokine 1 and IL-6 causing neutrophil infiltration and cell apoptosis [121].

chemokine production, neutrophil recruitment, reactive oxygen species production and increased collagen deposition, processes known to mediate NAFLD progression [100]. IL-17 excess in fatty liver is also related to hepatocellular carcinoma risk. Unconventional prefoldin RPB5 interactor (URI) is a chaperone involved in cell signaling, transcription processes, and DNA damage; it has been described in several tumors. Overexpression of IL-17-induced URI has been associated to NASH and hepatocellular carcinoma and its blockade decreased liver tumor risk.

NAFLD lacks specific treatment [95]. Patients are advocated to lose weight by hypocaloric diet and aerobic exercise, although this goal is rarely achieved [109]. IL-17 is relevant in the control of many immune-mediated diseases and therefore is an attractive candidate for NAFLD treatment. Nevertheless, the evidence is still scarce although promising. IL-17 blockade restores insulin resistance and prevents NAFLD inflammation in mouse models [110]. The genetic ablation of IL-17RA also alleviates NAFLD [110]. In another mice model, IL-17 blockade attenuated liver damage induced by lipopolysaccharide in baseline normal livers as much as in fatty liver, evaluated by transaminase levels as well as by liver biopsy. Statins have been shown to reduce liver inflammation in NAFLD [111]. Some studies highlight the immunomodulatory capacity of statins by inhibiting the differentiation of Th17 cells and decreasing its production [112,113]. Vitamin D levels are reduced in NAFLD, increasing its severity and fibrosis [114]. Vitamin D participates in modulation of IL-17 axis [114] and its supplementation in NAFLD reduces liver fibrosis, inflammatory response, and insulin resistance [115]. Considering the key role in NAFLD, IL-17 inhibitors could have a protective effect in NAFLD. In experimental models they improve hepatic steatosis [116] and could block the shift from steatosis to steatohepatitis [117], although clinical studies are still lacking.

4.1. Controversies

Blockade of IL-17 axis needs to show clinical benefit in NAFLD beyond basic investigation. Prospective, well-designed trials are eagerly awaited. The main focus is probably psoriasis patients with NAFLD, as they constitute a human model of IL-17-mediated systemic inflammatory chronic disease.

5. Cardiology

There is evidence that Th17 cell response has a relevant role in several cardiovascular diseases [118,119]. Interestingly, in a model of IL-17−/− mice, hypertensive response to angiotensin II infusion was not sustained as compared with C57BL/6J wild type mice, which indicates that IL-17 is required for maintenance of angiotensin II-induced hypertension [118]. Also, IL-17 deficiency abrogated vascular contraction of phenylephrine, with alterations in vascular tone thought to be at least partly mediated by alterations in superoxide production. IL-17 levels are increased in human hypertension as shown in a study of type 2 diabetic patients with and without hypertension, in whom IL-17 levels in normotensive individuals were significantly lower than in those with hypertension [118]. Therefore, it may be plausible that targeting IL-17 and Th17 cells might help to control blood pressure and preserve vascular function without affecting global immunity.

Over the past few years our understanding of the importance of adaptive immunity in acute coronary syndromes (ACS) has considerably increased. Profound abnormalities have been observed in specific subsets of CD4+T cells, including type 1 helper T (Th1) cells, CD4(+) CD28(null) T-cells, and naturally occurring regulatory T-cells (Treg cells) [120]. The relevance of IL-17 to human atherosclerosis remains poorly defined because of conflicting results in animal studies. While some studies have suggested a proatherogenic role for IL-17, an atheroprotective role for IL-17 through cross-regulation of IFN-γ-producing Th1 cells has also been proposed. IL-17 exerts proatherogenic effects by inducing the production of cytokines, chemokines, and matrix metalloproteinases. IL-17 also promotes G-CSF-mediated granulopoiesis and the recruitment of immune cells. Moreover, IL-17 induces apoptosis of endothelial cells and cardiomyocytes by activating caspase-3 and caspase-9, and up-regulating the Bax/Bcl-2 ratio [120]. The atheroprotective effect of IL-17 seems to be mediated at least in part by the regulation of other cytokines (reduction of IFN-γ and enhancement of IL-5) and by its inhibitory effect on VCAM-1 expression, an adhesion molecule mediating the accumulation of monocytes and T-cells within the lesions [120].

It has been shown that IL-17A contributes to myocardial ischemia/reperfusion (I/R) injury by regulating cardiomyocyte apoptosis and neutrophil infiltration (Fig. 5) [121].

In a mouse model of left coronary artery ligation and reperfusion, IL-17A was demonstrated to play a critical role in mediating I/R [122]. It was found that myocardial infiltrated γδ T lymphocytes, but not Th17 cells, were a major source of IL-17A. Anti-IL-17A monoclonal antibody treatment or IL-17A knockout markedly ameliorated I/R injury, which was associated with a reduction in cardiomyocyte apoptosis and neutrophil infiltration, but repletion of exogenous IL-17A induced the opposite effect. These data suggest a novel IL-17A-dependent pathway by which the immune system may influence the myocardial I/R injury. Control of IL-17A production may be of benefit for minimizing I/R-associated myocardial damage.

In a study that investigated the relationship between serum levels of IL-17 and the risk of cardiovascular events in 981 patients enrolled in a prospective French registry of myocardial infarction, serum levels of IL-17 were associated with the risk of all-cause death and recurrent myocardial infarction at 2 years, with levels of IL-17 below the median indicative of a worse outcome [123]. It was also shown that the effect of IL-17 remained significant after adjusting for known cardiovascular risk factors, C-reactive protein, and treatments including statins. IL-17 inhibited mononuclear cell adhesion to endothelium and reduced endothelial vascular cell adhesion molecule (VCAM-1) expression. At 2 years, 43% of death and myocardial infarction occurred in patients with low (below the median) baseline IL-17 and high (above the median) baseline sVCAM-1 levels compared with 12% in those patients with high baseline IL-17 and low baseline sVCAM-1. The corresponding

hazard ratio (HR) for event rates was 4.03 (95% CI 2.48-6.55) and remained significant in the Cox multivariate analysis. This study shows that elevated levels of IL-17 are associated with a better outcome in patients with acute myocardial infarction, supporting a protective regulatory role of IL-17 in coronary heart disease. Moreover, the highest risk of death and recurrent infarction observed in patients with low levels of IL-17 and high levels of sVCAM-1, indicates an important modulatory role of IL-17 on vascular inflammation [123]. In a recent study by Elnabawi and cols, they analyzed the total burden of atherosclerotic coronary artery plaques and the plaque subcomponents by coronary CT in 290 psoriatic patients. The plaque burden was significantly correlated with traditional cardiovascular risk factors and with the severity of the disease according to the PASI. A greater reduction in the non-calcified plaque burden and necrotic core was observed in the anti-IL17 treated group, compared to other biologic treatments (anti-IL 12/23 and anti-TNF alpha groups). These findings highlight the importance of systemic inflammation in coronary artery disease in psoriatic patients. The modulation of coronary plaque indices using biologic treatment with anti-IL17 in severe psoriatic patients shows an opportunity of reducing the cardiovascular risk in these patients [124]. Targeting the IL-17 pathways appears a promising therapeutic approach in the field of atherosclerosis and acute myocardial infarction [125].

On the other hand, IL-17A induces endothelial damage through increased apoptosis by decreasing the mitochondrial transmembrane potential and have a synergistic effect with TNFα on endothelial cells leading to pro-inflammatory and pro-thrombotic responses [126]. Recently, in a 52-week randomized, double-blind, placebo-controlled study (CARIMA) in patients with plaque psoriasis without cardiovascular disease, secukinumab showed a beneficial effect on cardiovascular risk as improved significantly endothelial function measured by flow-mediated dilatation [127].

IL-17A induces apoptosis in cardiomyocytes by increasing the pro- to anti-apoptotic protein ratio (B-cell lymphoma-2-associated protein X Bax/Bcl-2 ratio) [128] and through iNOS (inducible nitric oxide synthase) activation [129]. Also, it has been suggested that immune activation and genetic polymorphisms of IL-17 genes contribute to the pathogenesis and progression of heart failure. In a total of 1713 adult patients with congestive heart failure and 1713 age- and sex-matched controls, genotyping for promoter single nucleotide polymorphisms (SNPs), rs2275913 and rs8193037 in IL-17A and rs4819554 in IL-17RA was examined in order to determine the relationship between individual SNPs and the risk of congestive heart failure [130]. It was found that rs8193037 in IL-17A was associated with the risk of congestive heart failure after adjustment for multiple cardiovascular risk factors including age, sex, smoking status, diabetes, hypertension, and dyslipidemia, and this association being evident in both ischemic and non-ischemic heart failure. In addition, rs4819554 in IL-17RA was associated with cardiovascular mortality after a follow-up of 12.7 months. This study provided evidence for an association of rs8193037 in IL-17A with the risk of heart failure, and of rs4819554 in IL-17RA with the risk of cardiovascular mortality [130].

It is recognized that several immune-mediated chronic inflammatory diseases (IMIDs) such as Psoriasis, Rheumatoid Arthritis, Ankylosing spondylitis, Crohn, share co-morbidities including metabolic syndrome and accelerated atherosclerosis, that are associated with increased cardiovascular risks. They all are considered to harbor a low-grade systemic inflammatory state that might be responsible for insulin-resistance and increased cardiovascular co-morbidities. In fact, release of pro-inflammatory cytokines ie TNF, IL-17, IL-6 and adipocytokines from tissues into the circulation has been directly related with accelerated atherosclerosis in Psoriasis [131].

5.1. Controversies

The role of IL-17A in cardiovascular risk has been suggested in studies with cell cultures and in vivo studies. A relevant involvement of IL-17A has been postulated in the development and maintenance of arterial hypertension, endothelial dysfunction, myocardiocyte apoptosis and in the extent of myocardial infarction in ischemia/reperfusion models. Regarding IL-17A relationship with atherosclerosis, there are controversial aspects determined by its dual proatherogenic and antiatherogenic action, which in clinical models of chronic systemic inflammation could shift towards a preponderant proatherogenic effect based on its synergistic action with TNTα. More clinical studies are needed to explore the therapeutic effect of blocking IL-17A in relation to cardiovascular risk in patients with chronic inflammatory diseases such as psoriasis, psoriatic arteritis and ankylosing spondylitis.

6. Ophthalmology

A pathogenic role of Th17 cells in some ocular disorders, particularly uveitis, has been the focus of interest in recent years. Mucientes et al. [132] evaluated the possible influence of the IL-17A locus on susceptibility to non-anterior uveitis. To this purpose five IL-17A polymorphisms (rs4711998, rs8193036, rs3819024, rs2275913 and rs7747909) were genotyped in 353 Spanish patients with non-anterior uveitis and 1851 ethnically matched controls. A consistent association between two of the analyzed genetic variants, rs8193036 and rs2275913, and the presence of panuveitis and the diffuse form of the disease was found. These data agree with the elevated levels of this cytokine that are found in patients with uveitis, supporting a crucial role of Th17 cells in this pathology [132].

In Behçet's disease (BD) in which uveitis is characterized in its more severe form by posterior or panuveitis and retinal vasculitis, a study of 37 patients with BD and uveitis showed that IFN-γ, IL-17A, TNF-α, and high-sensitive C-reactive protein (hsCRP) were increased, with significantly higher levels of IFN-γ and TNF-α compared to healthy subjects, supporting a Th1 immune response [133]. The analysis of the cytokine profile in the subgroup of patients to whom serum samples were obtained during both active and inactive stages also revealed that IFN-γ and TNF-α were significantly increased during the active stage of the disease. Similarly, IL-17A was increased in patients with active uveitis compared to healthy controls. However, this increase was statistically significant only in those patients without treatment, suggesting the involvement of Th17 response in BD. Additionally, TNF-α also correlated with IL-17A in these patients, supporting the idea that BD is mediated simultaneously by both Th1 and Th17 responses [133]. Moreover, IFN-γ, TNF-α, and IL-17A levels were higher in patients without treatment than in those with pharmacological treatment in both active and inactive patients, and therefore it may be speculated that successful therapies should be able to prevent recurrent inflammatory attacks by keeping under control the circulating levels of these proinflammatory cytokines [133].

However, information on the efficacy of anti-IL-17A antibodies in the treatment of non-infectious uveitis is still limited. In patients with psoriasis (n = 36), rheumatoid arthritis (n = 52), and chronic non-infectious uveitis (n = 16), the efficacy and safety of AIN457 (a human antibody to IL-17A) at doses of 3–10 mg/kg given intravenously (i.v.) was investigated [134]. Efficacy for uveitis was assessed by the number of responders defined by either vision improvement or reduction in ocular inflammation or corticosteroid dose. Variable responses were obtained probably due to heterogeneity in small patient populations, differential pathogenic roles of IL-17A in these diseases, and the different involvement or activation of IL-17A-producing cells [134].

Results of three different randomized studies on the efficacy of secukinumab in heterogeneous populations of uveitis patients (118 patients with BD uveitis, 31 patients with active, noninfectious, non-BD uveitis, and 125 patients with quiescent, non-infectious, non-BD uveitis), were disappointing as there were no statistically significant differences in uveitis recurrence between the secukinumab and placebo groups in any study, although a beneficial effect of secukinumab in

reducing the use of concomitant immunosuppressive medication was recorded [135]. In a randomized, double-masked, dose-ranging, phase 2 clinical trial, with 37 patients with active non-infectious intermediate uveitis, posterior uveitis, or panuveitis who required corticosteroid-sparing immunosuppressive therapy, secukinumab iv (30 and 10 mg/kg) compared with a standard 300 mg subcutaneous dose, produced higher responder rates and remission rates [136]. Greater activity with i.v. dosing suggests that patients may not receive sufficient drug with subcutaneous administration, and that high-dose i.v. secukinumab may be necessary to deliver the drug in therapeutic concentrations [136].

The expression of Th 17-associated cytokines (IL-17, IL-23) has been studied in a small sample of 45 patents with dry eye disease [137]. Protein and conjunctival mRNA IL17A and IL6 levels were both significantly increased and correlated with ocular surface parameters. The expression of IL-23 was also significantly increased but did not correlate with ocular surface parameters. The expressions of IL-17A and IL-6 in tears have potential to be diagnostic biomarkers for dry eye disease [137]. In ocular surface inflammatory pathologies, namely pterygium and inflamed juvenile conjunctival nevus (IJCN), IL-17 was immunohistochemically detected in all IJCN specimens and in 84% of pterygia samples, suggesting that IL-17 blockade may have a potential role in management of these conditions [138].

In patients with type 2 diabetes mellitus and diabetic retinopathy (DR), the proportion of Th17 cells and IL17A production in peripheral blood mononuclear cell (PBMC) culture were significantly increased in patients without DR but decreased in those with DR, and were negatively correlated with body mass index, duration of diabetes, and glycated hemoglobin levels [139]. Additionally, vitreous fluid IL-17A levels were significantly elevated in patients with DR compared with controls. It seems that disturbances in Th17 cells and IL-17A levels might be associated with DR.

6.1. Controversies

Nowadays, the advent of highly effective and targeted biotherapies and the recent imaging technologies are improving the treatment and monitoring of patients with noninfectious uveitis. A personalized approach should take into consideration patient's characteristics and uveitis subtypes. Clinical and experimental observations suggest that iv IL-17A may be an attractive therapeutic target in patients with non-infectious uveitis. However, new molecules and the design of new clinical trials will be necessary to demonstrate its effectiveness in the treatment of noninfectious uveitis.

7. Neurology

The effect of IL-17 cytokines in central (CNS) and peripheral nervous system (PNS) inflammatory conditions is still not well defined. Multiple sclerosis (MS) is associated with encephalitogenic Th17 cells [140]. Recently, Th17 and IL-17 have been suggested to be involved in the pathogenesis of post-infectious Guillain-Barre syndrome [141]. High levels of IL-17 have also been linked to depression, a frequent comorbidity of several chronic inflammatory diseases, i.e. Psoriasis [131].

MS is a chronic inflammatory disease characterized by the destruction of myelin by peripherally activated autoreactive pathogenic T cells. In patients with MS early results showed increased expression of IL-17 in the brain at autopsy, and abundant IL-17-expressing cells in active CNS lesions [142,143]. In a seminal paper, Kebir et al [140] demonstrated in MS patients high IL-17R and IL-22R expression at BBB (blood brain barrier)- endothelial cells, and that *in vitro* treatment with IL-17A and IL-22 was able to induce BBB tight junction´s disruption. Recently Th17 subpopulations producing low amounts of IL-10 were identified as pathogenic in MS, and IL-10 production correlated with disease activity [144]. Further evidence for the pathogenic role of Th17 cells in MS derives from therapies. Trafficking of MOG-reactive Th17 cells from the periphery – where they are activated – into the CNS is a recognized early event in the development of MS. Natalizumab – a monoclonal antibody approved for severe RR MS directed to α4-integrin that blocks mononuclear cell migration across endothelial cells – is a highly active drug that exerts its effects by inducing peripheral accumulation of Th17, which returns to normal when relapses occur [145].

In the experimental autoimmune encephalomyelitis (EAE), a mouse model of the human MS where Th17-IL-17A induce disease, neutralization of IL-17 results in resolution [146]. An ongoing double-blind, placebo-controlled proof-of-concept trial with the IL-17A– specific antibody secukinumab in active relapsing-remitting multiple sclerosis has now provided preliminary results supporting the role of IL-17A in multiple sclerosis in humans, as they showed a substantial reduction of the number of new lesions revealed by magnetic resonance imaging (EudraCT number 2009- 011626-34) [147]. In this multicenter study carried out at 28 sites from the Czech Republic, Russia, and Ukraine, patients aged 18–55 years diagnosed with RRMS with stable disease at least 30 days before inclusion and not being currently treated disease-modifying drugs were eligible. Other inclusion criteria were the presence of one gadolinium (Gd) enhancing MRI lesion at screening/baseline or one relapse in the last year or two relapses in the last 2 years. The objectives of the study were to assess efficacy, safety and tolerability. The primary endpoint was the cumulative number of combined unique active lesions (CUAL) observed on brain MRI scans from week 4 to week 24. Patients (n = 73) were randomized 1:1 to secukinumab. Afterwards, patients were included in a 12-month open extension study, in which they received secukinumab 10/mg/kg i.v. every 4 weeks. MRI scans were obtained within 30 days prior to randomization, on a monthly basis during the treatment period, and at study completion. In relation to efficacy, a significant reduction in new MRI lesion activity was found, including reduction in cumulative CUALS and new T1-Gd^{+} lesions, with treatment benefits being apparent at week 12 and sustained through week 36. Also, a trend towards clinical relapse reduction in the secukinumab group was observed.

In Guillain-Barre syndrome (GBS), an heterogeneous peripheral neuropathy involving myelin and axons, recent immunological, genetic and gene expression studies suggest evidence towards the involvement of Th17 cells in the pathobiology of GBS. Han et al described increased circulating Th17 cell numbers, elevated CSF IL-17 concentrations and increased ROR-γt and STAT-3 expression in peripheral mononuclear cells from patients with GBS [141,148].

Psoriasis and other chronic inflammatory diseases such as inflammatory bowel diseases and Spondyloarthropathies (IMIDs, immunomediated inflammatory diseases) are now recognized as diseases in which a low-grade systemic chronic inflammatory state is associated with the development of co-morbidities, including increased risk of cardiovascular events and psychiatric disorders i.e depression and anxiety. In these patients, depression has been associated with increased plasmatic levels of pro-inflammatory cytokines (TNF, IL-17, IL-22) [131]. However, the role of IL- 17 in depression has not been well characterized. Of note, a recent study using mouse models of depression showed that administration of Th17 cells was directly correlated with depression sensitivity suggesting that the Th17 axis may play a role in neuro- immune interactions [149,150].

7.1. Controversies

The pathogenic role of IL17A both in experimental models of MS (EAE) and in MS is undisputed. Despite a small proof-of-concept trial has already been published (137), strong evidence on the long-term beneficial effects of IL17-blockade in MS is still needed. A clinical trial with Secukinumab was terminated early in 2016 based upon development of another anti-IL17 monoclonal antibody with better potential for treating MS patients (Clinical trial NCT01433250). Moreover, the

promising results with Siponimod improving inflammation, disability and brain atrophy in a large clinical trial in patients with secondary progressive MS stresses the importance of further exploring the relationship among inflammation and neurodegeneration to achieve the best treatment across the entire spectrum of the MS disease (EXPAND trial) [151]. Siponimod, an oral selective inhibitor of Sphingosine-1-phophatase receptors 1 and 5, has an anti-inflammatory effect on neuroinflammation because reduces pathogenic Th17 lymphocyte egress from peripheral lymphoid tissue into the brain. In addition, and because its ability to cross the blood-brain barrier, it can directly interact with non-lymphoid brain cells i.e astrocytes, microglia, oligodendrocytes and neurons, potentially exerting direct neuroprotective effects via routes beyond its anti-inflammatory effect [152].

8. Gastroenterology

Different studies during the past decade demonstrate that IL-17/IL-23 cytokines are overexpressed in Crohn's disease patients, playing a critical role in disease mechanisms. In a study of ileal biopsies from patients with active and inactive Crohn's disease (CD) and control subjects, lamina propria IL-17 and IL-23-positive cells were higher in patients with CD, both active and inactive, than in the controls. Furthermore, IL-17A mRNA expression was increased in biopsies from both patients with active or inactive disease, whereas fecal IL-17 mRNA was increased only in active disease [153]. In another study of tissue samples from patients with ulcerative colitis (UC), CD, infectious colitis, ischemic colitis, and healthy controls, IL-17 expression evaluated by immunohistochemical techniques was only present in IBD samples [19]. In inflamed mucosa from active UC and CD patients, IL-17 expression was detectable in CD3(+) T cells and CD68(+) monocytes/macrophages with a significant increase in the number of IL-17(+) cells in active UC and CD patients as compared with inactive patients. Although IL-17 was not detected in the sera from normal individuals, infectious colitis, or ischemic colitis patients, IL-17 levels were significantly elevated in IBD patients. In another study assessing intestinal biopsies from 40 patients with UC, 20 with CD, and 20 healthy controls, Th17 cells abundance and IL-17A, IL-21 and IL-22 expression were significantly increased in active IBD patients and correlated with disease activity index and endoscopic and histological score [154]. These results provide evidence about the important role of Th17 cells and Th17-related cytokines in mucosal damage and disease activity in IBD. A meta-analysis of UC and CD Genome-wide association studies (GWAS) in more than 75,000 cases and controls revealed a total of 163 loci that meet genome-wide significance thresholds in patients with IBD. An interesting finding was a strong association between variants in IL-23R with susceptibility to CD, thus confirming the implication of the IL-23/IL-17 axis in disease pathogenesis [155].

The efficacy of ustekinumab (a monoclonal antibody against IL-12/IL-23 p40) in Crohn's disease in different studies also supports the idea of the involvement of the IL23/IL17 axis in the pathogenesis of IBD [156]. Moreover, published results from an open-label extension study with risankizumab, a monoclonal anti- IL23p19, in patients with Crohn disease are promising [157].

Taking into account all these evidences, IL-17 neutralization, theoretically, could be effective in the treatment of patients with Crohn's disease. However, secukinumab, a human anti-IL-17A monoclonal antibody, was ineffective in a double-blind, randomized, placebo-controlled proof-of-concept study of 59 patients with moderate to severe CD (secukinumab 39, placebo 20) [158]. Unexpectedly, the trial was stopped prematurely because predefined criterion of futility was met ($\leq$ 90% probabilities that secukinumab reduces Crohn's Disease Activity Index by $<$ 40 points more than placebo). Surprisingly, higher rates of adverse events (*Candida* spp. infection) were observed in the treatment group. To explain secukinumab's lack of efficacy in IBD, it has been postulated that overgrowth of *Candida* spp. might be responsible for the worsening of IBD patients, [159]. Another possible explanation is that blocking IL-17A may interfere with the protective function of this cytokine in the intestine, i.e. maintenance of epithelial integrity, showing the high complexity of IL-17 biology [160]. Other approaches neutralizing IL-17 pathway in IBD patients have also failed. In a phase 2, randomized, double-blind, placebo-controlled, dose-ranging study in patients with moderate-to-severe CD and evidence of active inflammation, brodalumab (anti-IL-17RA antibody) provided disappointing results, with a disproportionate number of cases of worsening CD and no evidence of meaningful efficacy [161].

8.1. Controversies

Inhibition of IL-17 has been ineffective to induce remission in trials of patients with Crohn's disease despite strong evidences that IL-23/IL-17 axis plays an important role in disease mechanisms. IL-17 pathway regulation complexity and/or fungi overgrowth could explain lack of efficacy. Further in-depth immunological studies should investigate intestinal pathophysiology by setting targeted molecules in the context of its real biological network.

9. Hematology

Allogeneic stem cell transplantation (Allo-HCT) is a curative immunotherapy for patients with blood-related diseases [162], but graft-versus-host disease (GvHD) remains a major cause of transplant failure [163,164], and effective therapeutic options beyond systemic steroids are limited. Recently, murine transplant research has shown that in vitro differentiated Th17/Tc17 lineages cells alone could mediate GvHD [165]. Highly in vitro purified Th17 cells are capable of inducing lethal GvHD in a murine acute GvHD (aGvHD) model, hallmarked by extensive cutaneous and pulmonary lesions. The majority of these Th17 cells retained the ability to produce IL-17A in an INFγ-independent manner. Also, in a murine Allo-HCT model, targeted depletion of Tc17 cells (a subset of $CD8^+$ T cells) early after transplant protected from lethal aGvHD but failed to mediate graft-versus-leukemia effect [166], suggesting that targeting these cells would not increase the relapse risk.

A study of lesional skin biopsies in patients suffering from skin GvHD showed that distinct T-cell patterns characterized the acute and chronic forms of cutaneous GvHD [167]. Of note, chronic lichenoid GvHD showed a mixed Th1/Th17 response as evidenced by a predominance of Th1 (IFN-γ, IL-12/IL-23p40) and Th17 cytokines (IL-17, IL-23p19) and a relative increase of IL-17 and IFN-γ single-producing CD8+ T cells. These findings allow to more accurately distinguish between GvHD manifestations, and further confirms that Th17/Tc17 might play a key role in GvHD pathogenesis.

Over the last years several strategies such as B-cell depletion, JAK1/2 pathway inhibition, or the infusion of mesenchymal stem cells and regulatory T-cells have been developed to treat steroid refractory GvHD. In line with this, targeting Th17 differentiation and function with an anti-IL-17 monoclonal antibody might be a way to provide better control for some GvHD manifestations such as pulmonary and cutaneous. Nevertheless, concerns have been raised regarding the use of anti-IL-17 in the Allo-HCT setting, given the IL-10 dependent regulatory effect of Th17 in the gut and recent reports regarding the development of acute GvHD in IL-17 -/- knock-out murine model [168]. The inhibition of IL-17 in AlloHCT could be a potential therapeutic path to treat GvHD. To date, anti-IL-17 MoAb have not been used to treat AlloHCT patients and its role warrants further study.

10. Oncology

Recently, the inflammatory cytokine interleukin 17 (IL-17) and the IL-17-Th17 pathway have gained attention as promising therapeutic targets in the immune-oncology field. Many studies have shown high levels of IL-17 in gastric carcinoma, colorectal cancer, non-small cell lung cancer, breast, ovarian and hematologic cancers [169–175]. The

utility of anti-IL-17 mAb CJM112 alone or in combination with anti-PD-1 in multiple myeloma patients is being studied in a phase I clinical trial (NCT 03111992).

IL-17 is a double-edged cytokine that acts in a cancer-type depending manner as an anti- or protumor cytokine [176]. The oncogenic role of IL-17 is supported by studies that demonstrated an anti-apoptotic effect in mouse breast cancer models and sustaining self-renewal properties of ovarian cancer stem cells [174,177]. In addition, it has shown to decrease the presence of CD4 and CD8 infiltrating cells in tumor sites, to diminish the secretion of interferon gamma (IFN-γ) by CD8 T cells, to increase infiltrating $T\text{-}_{regs}$ and to promote angiogenesis [178], invasion and metastasis [179] recruiting tumor associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC) [180]. On the other hand, other authors have shown opposite effects. Indeed, the controversial role of IL-17 in cancer comes from the heterogeneity in how the IL-17 is measured in the different reports: as IL-17 mRNA or protein levels by western blotting and/or ELISA, as the presence of Th17 tumor-infiltrating T cell. However, the fact is that the role of IL-17 in different human cancers has been studied mostly in *in vitro* cell models and human xenografts while it is known that this cytokine is just one of the plethora of interleukins at the interplay between cancer and the stromal cell compartment that indeed, is secreted by several immune cells such as macrophages, dendritic cells, neutrophils, natural killers, CD8 and regulatory T cells, MDSC as well as Th17 cells.

Th17 cells are key players in inflammation and autoimmune disorders, but the clinical significance of their detection in the tumor microenvironment remains unclear. Actually, compared to conventional effector T cells, Th17 phenotype comprised low levels of granzyme B and activation markers HLA-DR and CD25 [181]. This observation is in favor of an impossibility to initiate cytotoxic killing. Although Th1 cells accumulate in the tumor microenvironment of most solid tumors as compared to samples of normal tissues, distinct functions regarding their ability to promote or to eliminate tumors have been reported, and it seems that this opposite functions depend on the features or the microenvironment, such as nature of the antigen-presenting cells, presence of TGF-β, IL-1β or IL-23. These cells can mediate antitumoral effects by their ability to recruit immune effector cells (cytotoxic T lymphocytes, natural killer cells, dendritic cells) into the tumor bed and they can promote tumor growth by means of angiogenesis (production of VEGF, angiogenic chemokines) and/or through immunosuppression (Treg conversion, myeloid-derived suppressor cell recruitment) [182,183].

10.1. Controversies

Targeting the Th17/IL-17 signaling axis in hematological and solid cancers is an exciting strategy in the immune-oncology field although it remains controversial. The dual role of IL-17 observed depends on many factors, current sources of knowledge are based in heterogeneous experimental cancer models and the lack of data regarding IL-17 and cancer in humans requires well-designed clinical trials to guarantee the safety and efficacy in cancer patients.

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Declaration of competing interest

JMGRM has been a lecturer and advisory board for Abbvie, an lecturer for Novartis, Takeda, Grifols, Merck Sharpe &Dohme.

LPG has receipt grants/research supports or participation in clinical trials (paid to Institution) from Abbvie, Almirall, Amgen, Boehringer Ingelheim, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB, has receipt of honoraria or consultation fees from Abbvie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi, UCB and has participated in a company sponsored speaker's bureau for Celgene, Janssen, Lilly, MSD, Novartis, Pfizer.

ED has been an advisory Board member, consultant, received grants, research support, participation in clinical trials, honorarium for speaking, research support, with: Abbvie/Abbott, Almirall, Amgen, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD-Schering-Plough, Celgene and Lilly.

JDC received consulting fees from Celgene, Janssen, Lilly, Mylan, Novartis, Pfizedr and UCB.

JLP has received lecturing and consulting fees from Janssen, Pfizer, Lilly, Novartis, Roche, Celgene, Bristol, Gilead, Sanofi and Biogen.

AOM has been an advisory board member and speaker for Abbvie and Novartis.

AA has receipt grants/research supports or participation in clinical trials from Abbvie and Roche, has been an Advisory Boards member for Abbvie, Novartis, Santen, Alimera and Allergan and speaker for Abbvie, Novartis and Alimera.

XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, Excemed, MSIF and NMSS.

NB received lecture fees from Abbvie, Merck, Janssen and Takeda and consulting fees from Janssen in the last year.

GO has been in a consulting or advisory Role: Bristol-Myers Squibb, Incyte, Novartis, Pfizer, received speakers' bureau from Bristol-Myers Squibb, Incyte, Novartis, Pfizer and travel, Accommodations and expenses from Bristol-Myers Squibb, MSD, Pfizer and Takeda.

CGV has received speaker honoraria from Novartis, Janssen, Lilly, Pfizer, MSD and Gilead.

MAGG received grants/research supports from AbbVie, MSD. Jansen and Roche and had consultation fees/participation in company sponsored speaker´s bureau from AbbVie, Pfizer, Roche, Sanofi, Celgene, Sobi, Novartis and MSD.

CVM and VMV are employees of Novartis Pharmaceuticals.

CGJ and EHM have none conflict of interest to declare.

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