Th17 Cells in Periodontitis and Its Regulation by A20

Ning Huang†, Hao Dong†, Yuqi Luo and Bin Shao*

State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China

Periodontitis is a prevalent chronic disease that results in loss of periodontal ligament and bone resorption. Triggered by pathogens and prolonged inflammation, periodontitis is modulated by the immune system, especially pro-inflammatory cells, such as T helper (Th) 17 cells. Originated from CD4+ Th cells, Th17 cells play a central role for they drive and regulate periodontal inflammation. Cytokines secreted by Th17 cells are also major players in the pathogenesis of periodontitis. Given the importance of Th17 cells, modulators of Th17 cells are of great clinical potential and worth of discussion. This review aims to provide an overview of the current understanding of the effect of Th17 cells on periodontitis, as well as a brief discussion of current and potential therapies targeting Th17 cells. Lastly, we highlight this article by summarizing the causal relationship between A20 (encoded by TNFAIP3), an anti-inflammatory molecule, and Th17 cell differentiation.

Keywords: T helper cells, Th17, inflammation, periodontitis, A20 (TNFAIP3)

INTRODUCTION

Periodontitis, influencing nearly 10%-15% people globally, is a common chronic disease featured by periodontal inflammation and alveolar bone destruction (1, 2). The pathogenesis of periodontitis mainly involves disease-associated oral microbiota, host inflammation, as well as environmental and genetic risk factors (3, 4). Ultimately, chronic and overwhelming inflammation causes periodontitis, which could only be terminated by tooth loss or therapeutic interventions. Recent studies have suggested a correlation between periodontitis and other systemic diseases including obesity, diabetes, hypertension, cardiovascular diseases and Alzheimer’s disease (5–9).

T cells are positioned critically in the pathogenesis of periodontitis, especially Th17 cells. Th17 cells are a lineage of CD4+T cells that are known for producing proinflammatory cytokine interleukin (IL)-17 (10). Induced by retinoid-related orphan nuclear receptor γt (RORγt, in man-made homologue RORC), Th17 cells recruit neutrophils, regulate chemokine receptors, initiate inflammation and bone resorption through pro-inflammatory cytokines such as IL-6, IL-17, IL-23 (11–13). Th17 cells also exacerbate inflammation further by recruiting Th17 cells (14, 15). Although Th17 cells act against microbial signals, especially in mucosal immunity, Th17 cells are inflammation enhancers that promote periodontal inflammation and bone resorption in the oral cavity (16). Accordingly, antibodies targeting IL-17 have protected mice from severe periodontitis, including diabetic ones (17, 18). Also, modulators of the Th17/T regulatory (Treg) balance, such as boldine, IL-35, IL-10 secreting B cells, calcitriol, showed efficacy in alleviating periodontitis (19–22). Beyond the oral cavity, IL-17 blockade also showed promising outcomes in treating immune diseases like psoriasis (23).
To restrict excessive inflammation in the oral cavity, the immune system has developed a set of restricting measures to attain timely termination of inflammation and maintain the holistic equilibrium. For example, the ubiquitination system modulates intracellular homeostasis through covalent enzymatic post-transcriptional modifications. Ubiquitin-editing enzymes activate, conjugate, ligate or remove polyubiquitin chains from their substrates enzymatically, thus deciding protein fate and regulating immune responses (24). A20 (TNFAIP3) is a ubiquitin-editing enzyme that has established its role as a potent anti-inflammatory molecule. A20 deubiquinates key factors of nuclear factor-κB (NF-κB), thereby blocking NF-κB pathway and arresting immune responses (25, 26). On the N-terminal of A20, ovarian tumor (OTU) domain enables A20 to deubiquitinate (27). While on its C-terminal, seven zinc finger (ZnF) domains confer A20 with ubiquitin-binding ability (28). In recent years, A20 displayed pleiotropic effects in cell death, tumorigenesis and autoimmune diseases (29–31). Hereinbelow, we discuss the regulatory role of A20 in Th17 cell differentiation and IL-17 function.

In this review, we summarized the pivotal role of Th17 cells in periodontitis as well as their modulation by cytokines and transcription factors. We also concluded the heterogeneity and plasticity of Th17 cells. Current therapies targeting Th17 cells are summarized as well. Moreover, as a team that focus on A20-related studies, we highlight this article by concluding the negative effect of A20 on Th17 cell expansion and IL-17 signaling, which could be a potential tool in treating periodontitis.

**DYSBIOSES AND DYSREGULATED INFLAMMATION DRIVE PERIODONTITIS**

The understanding of the aetiology of periodontitis has gone through different stages. Originally, it was thought to be a rather simple bacterial infection attributed to a small group of bacteria. However, later studies revealed the existence of influential factors other than microbiota, for example host reaction and environmental factors (3, 32–34). Put simply, the pathogenesis of periodontitis starts from gingivitis. The synergy between dysbiosis (changes or imbalance in the composition and abundance of oral microbial communities) and aberrant immune responses is the exact reason why gingivitis develops into periodontitis (35).

Physiologically, the oral cavity is always in a delicate balance between local immune activation and suppression (36, 37). However, under certain circumstances, the overgrowth of oral commensal microbiota leads to gingivitis, a destructive but reversible inflammatory disease. Then, depending on host susceptibility, some patients may suffer from the conversion to periodontitis, while others maintain long-term stability (38). In susceptible hosts, sustained gingival inflammation forms inflamed pockets in which gingival crevicular fluid provides essential nutrients (including abundant collagen decomposition products, serum exudates, etc.) for bacteria (34, 39). In addition, such inflammatory conditions create an anaerobic environment where anaerobic bacteria proliferate, finally leading to the overgrowth of commensal microbiota and dysbiosis (40, 41). Dysbiosis exacerbates inflammation and conversely, chronic dysregulated immune responses in turn facilitate dysbiosis by providing tissue decomposition as nutrients for bacteria, thus forming a positive feedback loop (35, 40) (Figure 1).

Of note, periodontitis could be independent of microorganisms. It was reported that germ free (GF) mice did not present alveolar bone loss even with *P. gingivalis* infection (42). Also, a combined application of therapeutic strategies targeting inflammatory response achieved better results than simple plaque removal, revealing the key role of host response in periodontal tissue destruction (43–46). Besides dysbiosis and dysregulation of immune responses, genetic and environmental factors are also crucial in the pathogenesis of periodontitis. Genetic polymorphisms may increase the risk of inflammatory disease varied by region and race/ethnicity (47). A recent study reported that in the Asian population, tumor necrosis factor (TNF)-α G-308A (rs1800629) polymorphism is linked with increased susceptibility to chronic periodontitis (48). Also, smokers are at least 50% more likely to develop periodontitis than non-smokers, with faster progression, severer deterioration, and poorer treating efficacy (49, 50). Weight gain may also be one of the risk factors for periodontitis, for clinical evidence suggests that obese people have a higher risk of periodontitis (51). Long-term psychological stress or anxiety leads to both worse periodontal conditions and a negative impact on the effectiveness of periodontal treatment (52, 53). In summary, periodontitis is a multifactorial chronic inflammatory disease mainly caused by dysbiosis, dysregulated immune system along with genetic and environmental factors.

**TH17 CELLS AT A GLANCE: BEYOND THE TH1/TH2 PARADIGM**

Currently, Th cells are commonly categorized into five major subsets: Th1, Th2, Th17, T-follicular helper (Tfh) and Treg cells (54). All these CD4+ T cells play important roles in host immune defence against harmful microorganisms as well as in inflammation diseases (54, 55). Here we will give a brief introduction on the discovery of Th17 cells.

In 1986, Mosmann and Coffman pioneered the classification of CD4+ T cells into two subsets: Th1 cells and Th2 cells (56). Immature CD4+ T cells differentiate into specific lineages of Th cells under the regulation of local cytokine milieu and transcription factors. IL-12 and interferon (IFN)-γ activate transcription factors signal transducer and activator of transcription (STAT)1, STAT4 and T-bet in CD4+ T cells, which favor the differentiation into Th1 cells (57, 58). Similarly, IL-2 and IL-4 promote the differentiation of Th2 cells by increasing the expression of STAT6 and GATA-3 (59, 60). The classic Th1/Th2 paradigm preliminarily reveals the diversity of CD4+ T cells in function. Th1 cells defend against intracellular organisms while Th2 cells targets extracellular pathogens (61, 62). Abnormal activation of Th1 cells and Th2 cells is also a key factor in the pathogenesis of many autoimmune diseases and inflammatory reactions.
The study of Th1/Th2 paradigm has helped to understand the pathogenesis of many diseases, including multiple sclerosis, psoriasis and so on (63, 64). However, a study on experimental autoimmune encephalomyelitis (EAE) raised certain doubts. EAE is a disease previously attributed to Th1 cells but blockade of Th1 cells failed to protect mice from disease progression (65). Consequent studies discovered a novel lineage of CD4+ T cells characterized by IL-17 production, beyond the Th1/Th2 paradigm (66–68). H. Park et al. and L. E. Harrington et al. pioneered the discovery of a new pedigree of Th17 cells, which filled some gaps in host immune response and the pathogenesis of autoimmune diseases (10, 69).

Th17 cell subsets were originally named after their main cytokine IL-17A. IL-17A also comes from γδT cells, natural killer T (NKT) cells and congenital lymphoid cells after sensing pathogen invasion or injury signals (70, 71). These cells are collectively called type 17 cells and are characterized by the expression of RORγt and IL-23R (11, 72). Th17 cells act as important defenders against pathogen invasion, especially fungal infections. This explains why patients with congenital defects of Th17 cells have higher susceptibility to fungal infections such as Candida albicans (73). Also, considerable studies have shown that Th17 cells play a pivotal role in immune-mediated inflammatory diseases, including periodontitis, psoriasis, rheumatoid arthritis and so on (74–76).

**TH17 CELL INVOLVEMENT IN PERIODONTITIS PATHOGENESIS**

T cells are the major immune cell population in oral mucosal compartments both in health and disease. In periodontitis, the level of Th17 cells rockets, which indicates a close relationship between Th17 cells and periodontitis (77, 78). However, the complex role of Th17 cells and IL-17 in periodontitis is still controversial. Yu et al. found that IL-17RAKO mice exhibited severer alveolar bone loss due to compromised chemokine expression and neutrophil migration (79). While Dutzan et al. reported the opposite conclusion in Cd4creStat3f/f and LckcreRorcfl/fl mice that deletion in Th17 cell differentiation exhibited significantly reduced alveolar bone resorption compared with wildtype (17). IL-17 also displayed gender-dependent effect as female mice are more susceptible to alveolar bone loss due to impaired P. gingivalis-specific antibody response and chemokine production (80). Also, patients with autosomal dominant high IgE syndrome (AD-HIES, present with congenital poor Th17 cell differentiation) showed reduced susceptibility to periodontitis and less alveolar bone resorption (81, 82).

Hereinbelow, we discuss how Th17 cells promote periodontal inflammation and bone resorption through the secretion of IL-17A, IL-17F, IL-21, IL-22 and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as the interaction between Th17 cells with other immune cells (12, 16, 83–85) (Figure 2).

**The Functions of Molecules Secreted by Th17**

**IL-17A**

IL-17A is considered the main cytokine in the pathogenesis of periodontitis. Although it has a limited ability to induce inflammation directly, IL-17A could exert powerful inflammatory effects through synergistic effects with other inflammatory factors (86–88). IL-17A acts on non-hematopoietic cells such as fibroblasts, epithelial cells and endothelial cells to promote the expression of many inflammatory cytokines, including IL-1β, IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), GM-CSF and TNF-α (10, 83). Meanwhile, IL-17A upregulates the expression of C-C motif ligand (CCL) 2, C-X-C motif ligand (CXCL) 1, CXCL2, CXCL5 and CXCL8 (88).

IL-17A further recruits more neutrophils and monocytes through these chemokines and enhances their survival and...
activity by releasing more GM-CSF (16, 88). Furthermore, as inducers of human Th17 cell differentiation, IL-1β and IL-6 cooperate with IL-17A to form a positive feedback loop that enhances the inflammatory effect of IL-17A (89, 90). Finally, IL-17A could directly promote the destruction of periodontal connective tissue and alveolar bone by inducing the production of prostaglandin E2 (PGE2), matrix metalloproteinases (MMPs) and NF-κB receptor activator ligand (RANKL) (16). RANKL has a fundamental role in alveolar bone destruction, as the binding of RANKL to its functional receptor NF-κB receptor activator (RANK) on the precursor of osteoclasts could promote the maturation and activation of osteoclasts. The decoy receptor osteoprotegerin (OPG) competes against RANKL and binds to RANK, thus inhibiting osteoclast differentiation and bone resorption (Figure 3) (87).

The IL-17A signalling pathway initiates a cascade of inflammation. Specifically, IL-17A acts as a ligand that binds to the IL-17 receptor complex (IL-17RA/IL-17RC) and recruits the binding protein Act1 through the SEF/IL-17R (SEFIR) domain of the tail conserved domain on IL-17R (91). Act1 contains a tumour necrosis factor receptor-associated factor (TRAF) binding motif and possesses E3 ligase activity, meaning it could recruit and ubiquitinate TRAF6. After TRAF6 activation, transforming growth factor β (TGF-β) activated kinase (TAK) 1 and inhibitor of NF-κB (IkB) kinase (IKK) complexes were recruited and activated, which trigger NF-κB and mitogen-activated protein kinase (MAPK) pathways, eventually promoting the expression of inflammatory mediators and the activation of osteoclasts (92, 93). At the same time, IL-17RA possesses a unique C-terminal activation domain, called CCAAT/enhancer binding protein β (C/EBP β) activation domain (CBAD) that participates in the activation of transcription factor C/EBP β. C/EBP β not only mediates and enhances the synergistic effect of IL-17 and TNF signal, but also up-regulates the expression of inflammatory mediators such as IL-6 (94, 95).

IL-21
IL-21, a member of the IL-2 cytokine family, is another cytokine secreted by Th17 cell, but its exact role is incompletely understood. In some experiments, the level of IL-21 in the serum and saliva of patients with chronic periodontitis significantly increased, and the level of IL-21 is down-regulated after periodontal treatment, suggesting that IL-21 may promote periodontitis (96, 97). In the absence of IL-6, the synergistic effect of IL-21 and TGF-β activates STAT3 to promote the development of Th17 cells, and inhibits the expression of Forkhead Box P3 (FOXP3) (98, 99). However, some studies suggested that IL-21 plays a dispensable role in riving the inflammatory effect of Th17 cells because IL-21- and IL-21R-deficient mice were still highly susceptible to EAE (100, 101). Lastly, a specific study, in which IL-21 induces IL-10 expression in B10 cells and results in less alveolar bone loss, suggested that IL-21 inhibits inflammation (102). More experiments are needed to examine whether IL-21 is the driver/inhibitor/bystander of periodontitis.
IL-22 is a member of the IL-10 cytokine family. IL-22 receptor is composed of the IL-22R1 subunit and the IL-10R2 subunit, shared with IL-10. Even though IL-10 downregulates pro-inflammatory cytokine expression, IL-22 often fails to do so. This is mainly because the expression of human IL-22R1 is often limited to epithelial cells and endothelial cells, while immune cells usually lack the expression of IL-22R1 (103).

IL-22 is pro-inflammatory as it enhances the effects of co-acting pro-inflammatory factors such as TNF-α and IL-17 (104, 105). Specifically, IL-22 binds with IL-22R1 to form a complex that binds to IL-10R2, which usually activates the Janus kinase (JAK)-STAT signaling pathway, especially STAT3 as the main signal transduction pathway (106). In addition, IL-22 could also directly promote the expression of inflammatory mediators like MMP-1, resulting in connective tissue destruction and bone loss.

**FIGURE 3** | IL-17A drives alveolar bone resorption through the RANKL/OPG axis. The promotion of bone resorption by Th17 cells involves the joint action of a triad of proteins including RANKL, its functional receptor RANK and its decoy receptor OPG. (A) Cytokines including TGF-β, IL-1β, IL-6, IL-23, etc. promote the differentiation of Th17 cells and production of IL-17A. (B) Osteoblasts generate RANKL to bind to its receptor RANK on osteoclast precursor cells, as well as OPG to antagonize RANKL. (C) IL-17A-induced B cells and MSCs activation also promote RANKL production. (D) Osteoclast precursor cells differentiate and fuse into mature osteoclasts that causes alveolar bone resorption. (E) IL-17A mediates a proinflammatory M1 macrophage response which would be inhibited by IL-10, while IL-10 promotes M2 macrophage polarization. (F) M1 macrophages induce the production of proinflammatory cytokines such as IFN-γ and IL-6 to exacerbate alveolar bone loss. OPG, osteoprotegerin; TGF-β, transforming growth factor-β; MSC, mesenchymal stem cell; IFN, interferon.
resorption (107, 108). Recent studies have revealed a positive correlation between the IL-22, RANKL expression and the severity of periodontitis (109, 110).

**GM-CSF**

GM-CSF acts on dendritic cells (DCs) and monocytes to promote the production of inflammatory factors such as IL-6, IL-23, facilitating differentiation of Th17 cells (111). Particularly, IL-23 in turn promotes GM-CSF production and forms a vicious cycle (112). Recent studies have shown that the role of GM-CSF in inflammation and bone loss may be underestimated. In a mouse model of experimental autoimmune uveitis (EAU), GM-CSF-driven eosinophil inflammation dominates the development of EAU without IL-17 and IFN-γ (113). GM-CSF expression is downregulated at the presence of IL-17A, whereas IL-17A deficiency would lead to the upregulation of GM-CSF and inflammatory reaction (114). Further experiments confirmed that IL-17A induced IL-24 through autocrine pathway, downregulating IL-17F and GM-CSF expression through suppressor of cytokine signalling (SOCS)1 and SOCS3 (114). The rise of GM-CSF may explain, to some extent, why the use of anti-IL-17A monoclonal antibodies alone aggravates symptoms seen in inflammatory bowel disease (IBD) (115).

**Synergistic Effects of Th17 With Other Immune Cells**

**Neutrophils**

Neutrophils are now considered the vital cellular regulator of Th17 response in periodontitis. Excessive neutrophil accumulation in periodontium provokes inflammation, as the number of neutrophils is positively correlated with the severity of periodontitis (116–118). Neutrophils not only release reactive oxygen species (ROS) and MMPs to directly damage connective tissue, but also interact with adaptive immune cells, especially Th17 cells, to induce bone resorption (119, 120). Chemokine CCL2 and CCL20 produced by neutrophils recruit Th17 cells and facilitate their chemotaxis to the inflamed sites (121). IL-17, induced by neutrophils, also cooperates with IL-1β to increase the expression of CCL20 in human gingival fibroblasts and further recruit Th17 cells (122). As mentioned before, Th17-induced GM-CSF recruit neutrophils as well, eventually forming a feedback loop that leads to mutual recruitment.

Under physiological conditions, mutual recruitment ends up as the inflammation subsides. Phagocytosis of apoptotic neutrophils could inhibit the expression of IL-23 of phagocytes and then down-regulate the production of IL-17 and G-CSF, so that neutrophils decrease concomitantly with the regression of inflammation (123). Intriguingly, patients with leukocyte adhesion deficiency type I (LAD-I) have impaired leukocyte function but they still have a higher risk of periodontitis. The underlying mechanism could be the breakdown of the neutrophil regulation feedback circuit. Due to the lack of inhibition of IL-23 expression in LAD-I patients, excessive accumulation of IL-17 in periodontium eventually led to alveolar bone injury (124).

**APCs**

Antigen-presenting cells (APCs) present antigens and drive differentiation of Th cells, linking the innate immune response to the adaptive immune response (125, 126). Previous studies have demonstrated that periodontal pathogens stimulate APCs to upregulate the expression of markers that facilitate the proliferation of Th17 cells (122, 127). DCs principally mediate the adaptive immune response in periodontitis. Monocytes and macrophages are involved in instructing Th17 cell differentiation as well. Although their concentrations in healthy gingiva are relatively low, APCs increase significantly in patients with periodontitis (128).

Monocytes recognize *P. gingivalis* through toll-like receptors (TLR)2/4, and then upregulate the expression of IL-1β and IL-23 to induce Th17 cell differentiation (127). Also, Delta-like ligand 4 (Dll-4) expression in monocytes is upregulated by *P. gingivalis* lipopolysaccharide (LPS) to promote Th17 cell response (129). Periodontal pathogens also upregulate CDB6 expression and induce monocyte differentiation into macrophages (127). As for macrophages, LPS- and IFN-γ-activated macrophages were induced by CCL21 (which shows up-regulation in periodontitis tissues). These macrophages elevate the expression of both CCR7 and cytokines such as IL-6 and IL-23, which drive the differentiation of naive T cells into Th17 cells and enhance osteoblast production (130, 131).

**Induction and Enhancement of Th17 Cell by *P. gingivalis***

*P. gingivalis* is a gram-negative anaerobe which has been implicated as a keystone pathogen that contributes to periodontitis (132). Previous studies suggested that *P. gingivalis* interacts with APCs to induce Th17 cell differentiation (126, 127). It has been demonstrated that the interaction between *P. gingivalis* and host DCs induces the production of a series of inflammatory factors including IL-17, IL-1β, IL-6, IL-23 etc., which enhances and stabilizes the differentiation of Th17 cells (126). In addition, independent of APC activation in vitro, *P. gingivalis*-LPS promotes Th17 cell differentiation directly through TLR2 signalling. It also enhances IL-17-mediated bone resorption by the up-regulation of transcription factors such as RORC as well (133, 134).

Differed in their ability to induce Th17 cell differentiation, *P. gingivalis* can be classified into virulent (*P. gingivalis* ATCC33277) and avirulent strains (*P. gingivalis* W83) (135). Compared with avirulent strains, LPS from virulent strains showed a higher induction of IL-1β and IL-6 as well as higher expression of RORC and IL-17, promoting Th17 cell differentiation more effectively (126, 134).

**REGULATORS OF TH17 CELLS DIFFERENTIATION**

**Regulatory Roles of Cytokines and Transcription Factors**

Similar to that of Th1/2 cells, the differentiation of Th17 cells is induced by the synergistic action of STAT3 and RORγt which are regulated by local environment and cytokines (12). A complex collection including TGF-β, IL-1β, IL-6, IL-23, etc. affects the
TGF-β

Although still under debate, the current view is that at initial differentiation stage, TGF-β drives CD4+ T cells to differentiate into Th17 cells and Treg, rather than Th1/2 cells, by inducing the expression of RORγt and FOXP3. Subsequent differentiation depends on the activation of the mutually antagonistic STAT3 (which promotes Th17 differentiation) and STAT5 (which promotes Treg differentiation) (11, 137–139).

TGF-β regulates Th17 cells by both canonical (small mother against decapentaplegic (SMAD)-dependent) and non-canonical (SMAD-independent) pathways (140, 141). Members of the SMAD family are the substrates of TGF receptor signaling and they decide the consequent effect. TGF-β receptor signaling regulates SMAD2 and SMAD3. Activated SMAD2/3 then depends with SMAD4, and they finally bind to DNA together to activate or repress Th17 cell transcription, which depends on the different phosphorylation states of SMAD2 and SMAD3 (140, 142). Phosphorylated SMAD2 positively regulates Th17 differentiation by STAT3 activation and the synergistical effect between STAT3 with RORγt. While unphosphorylated SMAD3 binds to RORγt and then inhibits its transcriptional activity (142). Recent studies found that SMAD4 itself does not directly regulate Th17 cell differentiation. Instead, SMAD4 interacts with other transcriptional modulators to perform regulatory functions. For example, SMAD4 recruits and mediates SKI which possesses the real suppressive effect in Th17 cell activation (143, 144). Additionally, TGF-β regulates Th17 cell differentiation through SMAD-independent pathways such as NF-κB pathways and MAPK pathways (140, 141). Recent studies on the effects of TGF-β on Th17 cells have concentrated more on the heterogeneity and plasticity of Th17 cells, which we describe below.

IL-1β, IL-6, and IL-23

IL-1β regulates Th17 differentiation through multiple mechanisms. IL-1β promotes Th17 differentiation by excising FOXP3 exon 7 (147). IL-1β enhances AKT-mTOR signaling pathway which is essential for the survival and proliferation of polarized Th17 cells. AKT, glycogen synthase kinase 3α (GSK3α) and IKKα form a complex in which IKKα is negatively regulated by GSK3α. IL-1β activates IKKα and impairs the function of GSK3α, thus leading to AKT-mTOR activation (148). IL-1β activates DCs and enhances IL-17 secretion by Th17 cells in a CD14-dependent manner (149). IL-1β downregulates SOCS3 to enhance the amplitude and duration of STAT3 phosphorylation induced by IL-6 and IL-23 (150). IL-1β synergizes with IL-6 to promote Th17 cell differentiation and proliferation through direct RORγt expression and CD4+ T cells (89). In the absence of IL-6, excessive IL-1 signaling enhances Th17 cell responses by downregulating TGF-β-induced Foxp3 expression (151).

IL-6 binds to IL-6R (composed of IL-6Rα and gp130) and phosphorylates the JAK family via gp130 which then activates STAT3, whereas suppressing the activation of STAT1 which would inhibit Th17 cell differentiation (152, 153). IL-6 also induces IL-23R expression in naive T cells through the binding of STAT3 to IL23R locus, allowing IL23 to participate in late Th17 differentiation despite its initial absence due to the lack of IL-23R expressed on naive T cells (154). After IL-23R upregulation, the IL-23 signaling pathway activates STAT3 via the JAK family (155). IL-6 and IL-23-activated STAT3 up-regulates the expression of Th17 marker gene Rorc, producing RORγt that interacts with IRF4, BAFF and other transcription factors to up-regulate the expression of Th17 cell lineage markers such as IL-17A, CCR6 (11, 156). STAT3 also regulates the expression of Th17 differentiation-related genes including Il17a, Il17f, Il21 and Ibelra as well as cell survival and proliferation genes like Bcl2, Fos and Jun (83, 156).

IL-2

IL-2 possesses a suppressive function in Th17 cell differentiation. IL-2 activates STAT5 and then enhances the expression of FOXP3, impeding the binding of STAT3 to the Il17a promoter and antagonizing transcription factors such as RORγt and Runt-related transcription factor (RUNX) 1 via JAK1/3 (157). In addition, higher FOXP3 mRNA expression was also speculated in periodontitis accompanied by increased RANKL and Th17-related genes mRNA levels, suggesting self-restraint of the host inflammatory response (158, 159). Low-dose IL-2 treatment is reported to be beneficial to the balance of Th17/Treg cells in other inflammatory diseases like SLE and arthritis (160, 161). However, it is also noted that IL-2 depletion resulted in higher levels of apoptosis in Th17, as low levels of IL-2 produced by Th17 cells mainly promote the expansion of Th17 cells (162). More experiments are needed to explore the mechanisms underlying the effect of IL-2 on Th17 cell differentiation.

Heterogeneity and Plasticity of Th17 Cells

Intriguingly, not all Th17 cells boost inflammation and not all Th17 cells exacerbate inflammation through IL-17A. The molecular underpinning for such biological behaviour is the heterogeneity and plasticity of Th17 cells. Heterogeneity means that different Th17 subsets display different levels of pathogenicity, namely immunoregulatory IL-10+ Th17 cells and pro-inflammatory Th17 cells (163, 164). Plasticity means that Th17 cells possess the ability to trans-differentiate into phenotypes other than IL-17+ Th17 cells and express cytokines typical of other lineages (164).

Researchers believe that it is the cytokine milieu that determines Th17 cell phenotype. As previously stated, pathogenic Th17 cells are induced in IL-1β, IL-6 and IL-23 condition or in IL-6 and TGF-β3
condition (136, 165). However, non-pathogenic Th17 cells are differentiated by TGF-β1 or IL-6 (136, 166). Single-cell RNA sequence technology unveiled the transcriptional signatures of non-pathogenic and pathogenic Th17 cells. Pathogenic Th17 cells express more pro-inflammatory genes module including Il23, IL-22, Il17a, and Il17f, while non-pathogenic Th17 cells upregulate the expression of immune suppressive genes like Il10, Il4, Ahr and c-maf (167, 168). Their differences in pathogenicity explain opposite results shown in clinical trials targeting IL-17A signals in different expression of immune suppressive genes like Il10, Il4, Ahr and c-maf (167, 168). Their differences in pathogenicity explain opposite results shown in clinical trials targeting IL-17A signals in different diseases (115, 169, 170). Of note, c-Maf is indicative of pathogenicity because it regulates IL-10+ Th17 cell transcription via the MAPK pathway (163, 171). In other words, pathogenetic Th17 cells expresses less c-Maf compared with non-pathogenetic Th17 cells.

Th17 cells could also be inverted into an anti-inflammatory phenotype termed Th17-derived Tr1-like cells (exTH17) cells, which is induced by TGF-β1 via SMAD3 and aryl hydrocarbon receptor (AHR) (172). The inversion is related to Th17 cells plasticity, as evidences accumulate that Th17 cells seem to be unstable terminally differentiated cells (173, 174). Th17 cells are now considered to have the potential for phenotypic trans-differentiation into mainly Th17/Th1 cells, Th17/Th2 cells and even Th17/Treg cells, which may be altered by co-expression of CD4+ T cell lineage transcription factors (164, 175).

Recently, new breakthroughs have been made in the study of Th17 cells plasticity. Th17 cells may transform into Th1-like CXCR3+ Th17 cells (Th17.1 cells) under the regulation of IL-12 and IL-23. Interestingly, the absence of TGF-β1 not only promotes pathogenic Th17 cells, but also upregulates T-bet expression and shows much higher plasticity in transitioning into Th1-like Th17 cells, because early TGF-β1 suppression on T-bet is relieved (176). The expression of RUNX1 in Th17 cells could be enhanced by IL-12 stimulation and then binds to the Ifng locus in a T-bet-dependent manner, thus showing a phenotype that secretes IFN-γ (177). Namely, classical Th17 cells mainly express IL-17A, while Th17.1 cells develop into IL-17A+ IFN-γ+ cells or IL-17A+ IFN-γR2 cells (174).

Th17.1 cells show stronger pro-inflammatory properties, supported by higher proliferation ability in response to T cell receptor (TCR) signals, higher GM-CSF, CCL20 and IL-22 production (178, 179). A latest study, tracking the plasticity of Th17 cells in periodontitis model, suggested that the transformation of classical Th17 cells to ex-Th17 cells occurs during the conversion from acute inflammation to chronic inflammation (180). The dysbiosis caused by P. gingivalis may drive this transition through the increment of IL-17A in the early stage and the dominant expression of IFN-γ in the later stage (180).

Current and Potential Therapies Targeting Th17 in Periodontitis

Given the essential role of Th17 cells in periodontal inflammation and alveolar bone loss, it is conceivable that targeting Th17 cells and related key molecules is of great potential. Here we briefly describe some experimental therapies focusing on Th17 modulators, along with their results.

IL-17 acts as the main cytokine in the pathogenesis of periodontitis, and intervention experiments targeting IL-17 achieved positive results. Suppressed IL-17 expression significantly reduced alveolar bone resorption occurs in mice (17). Inhibiting RORγt and then down-regulating IL-17 expression via GSK805 or curcumin attenuated alveolar bone loss (17, 82). Beyond periodontitis, therapies targeting IL-17/IL-17R to treat autoimmune diseases such as psoriasis have achieved positive results (181). In a phase III, randomized double-blind placebo-controlled study using Brodalumab (a monoclonal antibody against IL-17RA) on moderate-to-severe plaque psoriasis, more than 70 percent of patients achieved a 75% reduction in psoriasis area severity index at 12 weeks, which is much higher than the placebo group (182). As previously mentioned, however, it was also reported that IL-17RAKO mice exhibited profound alveolar bone destruction for impaired chemokine expression and neutrophil migration (79). More studies targeting IL-17/IL-17R are required to investigate the exact mechanisms. Also, derived clinical trials aiming at periodontitis are essential for verifying the therapeutic effects.

IL-6 and IL-23 support the survival and expansion of Th17 cells (154). Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody which binds to human IL-6R and inhibits IL-6 signaling (183). TCZ treatment alleviated periodontal inflammation in patients, compared with those without TCZ therapy (184–186). As to IL-23, a case report claimed that systemic usage of ustekinumab, a monoclonal antibody blocking the p40 subunit of IL-23, resolved inflammatory lesions in a patient with LAD-I (187). JAK is a pathway downstream of IL-6. Patients who received tofacitinib, an inhibitor for JAK, also showed reduced periodontal inflammation (188).

MicroRNAs (miRs) act as vital regulators of Th17 differentiation and periodontal inflammation (189, 190). MiR-155 up-regulates Th17 responses and enhances osteoclastogenesis, while exosomal miR-155-5p from periodontal ligament stem cells (PDLSCs) could be transferred into CD4+ T cells and then decrease RORC expression, alleviating inflammatory microenvironment (191, 192). More studies are needed to explore the exact effects and mechanisms of miRs on regulating Th17 differentiation in periodontitis.

Some studies comment deubiquitylating enzymes (DUBs) as potential modulators of periodontitis progression because DUBs modulate IL-17 signaling by TRAFs. In particular, A20 is a protein that possesses DUB and regulates Th17 differentiation and IL-17 function (27). As several studies have demonstrated the anti-inflammatory effects of A20 especially via regulating Th17 differentiation, we consider A20 as a promising therapeutic target for periodontitis treatment (193–195). Hereafter, we focus on recent advances and regulatory mechanisms of A20 in modulating Th17 and IL-17.

A20: NOVEL THERAPEUTIC TARGET BY TH17 AND IL-17 MODULATION

Ever since it was first identified in 1990 as an inhibitor of NF-κB pathway in response to TNF, A20 has established its role as a
potent anti-inflammatory molecule, mainly attributed to its ubiquitin-editing function (25). On the N-terminal of A20, OTU domain deubiquinates K48 and K63-linked ubiquitin chains, the former target substrates for proteasomal degradation, whereas the latter often save targets from degradation (27). On its C-terminal, ZnF4 interacts with K63-linked ubiquitin chains and ZnF7 binds with M1-linked ubiquitin chains (196, 197). As a ubiquitin-editing enzyme, A20 restricts excessive inflammation mainly by deubiquitinating TRAF6, thereby blocking NF-kB pathway and arresting immune responses (26). In recent years, A20 has displayed pleiotropic effects in cell death, tumorigenesis and autoimmune diseases (29–31). Hereinbelow, we discuss the role of A20 in Th17 cell differentiation and IL-17 function.

A20 Inhibits Th17 Cell Expansion Through Diminished IL-6 Production

It is established that Th17 differentiation is dependent on cytokines like IL-6, IL-23, IL-17, the production of which relies on NF-kB signaling pathway that exaggerates inflammatory signals. As a negative regulator of NF-kB signaling pathway, the inhibitory role of A20 on cytokine production account for the increase of Th17 cells observed in A20-deficient models.

NF-kB pathway is a ubiquitous signaling pathway that modulates cell proliferation, immune responses, necroptosis, and so forth. Considerable attention has been paid to its role in tumorigenesis and inflammatory diseases (198, 199). After being initiated by pathogens, pro-inflammatory cytokines and others, IKK complex phosphorylates IxB and the latter undergoes proteasomal degradation (26). The subsequent translocation of NF-kB into the nucleus then activates NF-kB-related genes and produces, including but not limited to, pro-inflammatory cytokines such as IL-1, IL-6 and TNF, growth factors, chemokines, as well as inhibitors of NF-kB pathway like IxBz and A20 to avoid excessive inflammation (26).

A20 deubiquinates IKKα (also known as NF-kB essential modulator, NEMO) and TRAF6, an E3 ubiquitin ligase that is vital in the activation of IKK complex (200–202). The activation of IKK complex terminates NF-kB pathway and dampens NF-kB-mediated inflammation, exaggerating inflammation and elaboration of pro-inflammatory cytokines like IL-6, TNF. By the same token, A20 also dampens MAPK (especially JNK) activation through TRAF6 deubiquitylation (27, 203). Therefore, A20 depletions in human macrophage-like cells (THP-1) and in mice bone marrow derived macrophages lead to increase in cytokine production in vitro (194). Consistently, partial loss of A20 in mice show severer alveolar bone loss, more infiltration of immune cells, more pro-inflammatory cytokines including IL-6, IL-23, IL-17, and these mice display prolonged NF-kB activation (194).

The postulation that deficiency of A20 leads to a plethora of inflammatory IL-6 that drives Th17 differentiation has been confirmed in an arthritis-related study where A20 inhibits Th17 cell differentiation through IL-6 in mice lacking A20 in their bone marrow mesenchymal stem cells (BM-MSCs) (138, 204). The fact that A20 restricts IL-17 signaling and the concomitant decrease of its own implicates a negative feedback loop that maintains an equilibrium between inflammatory responses and homeostasis, avoiding excessive tissue damage and autoimmune disorders.

ZnF7 Motif in A20 Restricts Th17 Cell Proliferation

Hereinbefore, A20 possesses a ZnF7 motif on its C-terminal that is capable of binding with M1-linked ubiquitin chains (28). Research has shown that A20 represses inflammatory diseases through its ZnF4 and ZnF7 motif synergistically in a non-catalytic way (205). Mouse model A20^{ZnF7/ZnF7}, harboring a point mutation in C103 that disabled its ZnF7 motif, displayed an elevation in IL-17-expressing T cells, compared to its wild type littermates (205). As an array of studies showed that commensal bacterium is crucial to Th17 in arthritis, gastrointestinal tract and skin, A20^{ZnF7/ZnF7} were further bred in germ-free conditions this time to interrogate the relationship between Th17 cell expansion and commensal microbe colonization, however results did not show any causal relationship (36, 205–207). Th17 cell proliferation in the human gingival oral mucosal barrier is also independent of commensal bacterium (37). Therefore, ZnF7 motif might be a plausible target for therapeutic interventions although the underlying mechanism warrants further investigation at molecular and cellular levels.

A20 Binds to the C-Terminal of IL-17RA and Downregulates IL-17 Signaling

The IL-17 family includes ligands IL-17A to IL-17F that bind to IL-17RA to IL-17RE. IL-17 receptor is a heterodimer composed of IL-17RA and IL-17RC, both of which contains a SEFIR domain that is conserved in the IL-17R family (95). Upon IL-17 activation, SEFIR domain binds with adaptor protein Act1, which also contains a SEFIR domain, through homotypic interactions, thereafter, serving as a docking site for TRAF proteins (208). Specifically, Act1 recruits TRAF6 and triggers K63- ubiquitylation with the help of E3 ligase activity of Act1 (203, 209). Ubiquinated TRAF6 leads to the activation of IKK complex, subsequent phosphorylation and degradation of IxB pave the way for the initiation of canonical NF-kB pathway and promotes transcription of pro-inflammatory proteins such as cytokines, chemokines, and A20 (210). On the C-terminal of IL-17RA, CBAD is indispensable to the activation, translation and phosphorylation of C/EBPβ and negatively controls IL-17-induced signaling (27). CBAD contains a TRAF consensus site that helps TRAF3 replace Act1, ultimately mitigating IL-17R signaling.

It is substantiated that A20 binds to CBAD in IL-17RA, albeit not SEFIR domain, through anaphase promoting complex protein 5 (AnapC5 or APC5) which is known for its role in regulating cell cycle (211) (Figure 4). During this process, APC5 serves as an adaptor protein that facilitates the binding of A20 to inhibitory domain CBAD in IL-17RA and this interaction between A20 and CBAD ceases IL-17 receptor signaling.
Apart from being the end-product of Th17 cell secretion, IL-17 is capable of synergizing with IL-1β to promote CCL20 in human fibroblasts, consequently recruiting more Th17 cells and forms a feedback loop (212). As a matter of fact, Th17 cells also induces CCL20 and exaggerates its own pro-inflammatory effects (212). A20 mediates this feedback negatively by restricting IL-1β.

Unlike in GI tract and skin, the differentiation of Th17 cells in the oral cavity is independent of IL-1β, but IL-1β still appears critically positioned in the etiology of periodontitis, especially in immunomodulation and bone resorption (37, 213). IL-1β activates endothelial cells and promotes the adhesion of eosinophils, which exaggerates inflammation (214). IL-1β promotes the production of RANKL, which is vital to bone resorption as stated before (215). IL-1β also upregulates the formation and bioactivity of osteoclasts eventually leading to alveolar bone resorption (216). The secretion of IL-1β could be divided into two steps. Firstly, in response to microbial signals, pattern recognition receptors (PRRs), normally containing pyrin and/or caspase activation and recruitment domain (CARD), secrete pro-proteins like pro-IL-1β and pro-IL-18 through NF-κB pathway (217). Secondly, PRRs recruit the cysteine protease caspase-1 directly or indirectly through apoptosis-associated speck protein containing a CARD (ASC) (217). Caspase-1 cleaves inactive pro-proteins proteolytically and confer them with bioactivity but this requires a prior activation signal (218). An array of studies has confirmed that this activation signal is provided by inflammasomes, a multiprotein signaling complex assembled by members of the nucleotide-binding domain (NOD) and leucine-rich repeat containing (LRR) (NLR) family or the pyrin and HIN-domain (PYHIN) family (219).

In the case of IL-1β, a member of NLR family called NLR and pyrin domain (PYD)-containing protein 3 (NLRP3), along with caspase-1 and ASC, assemble into NLRP3 inflammasome (220). The bioactivity of NLRP3 inflammasome calls for two steps, priming and activation. The priming of NLRP3 inflammasome
requires microbial signals like NF-κB-dependent TLRs or TNF but there still lacks a unified theory on the secondary activation signal (219). Current studies suggest that the rise in extracellular ATP activates P2X7 and this triggers K⁺ efflux, eventually activating NLRP3 inflammasome (221).

As a pathological contributor to oral diseases, NLRP3 inflammasome activates caspase-1 and caspase-1 matures pro-inflammatory cytokines IL-1β and IL-18 (222). Meanwhile, NLRP3 also induces pyroptosis, a type of inflammation-associated cell death, by cleaving the N-terminal of gasdermin D (GSDMD) and forming a pore on the cell membrane (223). NLRP3 also promotes alveolar bone resorption through osteoclast differentiation (224). The level of NLRP3 inflammasome mRNA and its related proteins are increased in periodontitis and gingivitis, which corroborates a negative role of NLRP3 in the oral cavity (225).

Considerable research has focused on the inhibitory role of A20 in NLRP3 inflammasome maturation (Figure 5). First of all, A20 downregulates NF-κB signaling pathway, which directly limits the production of pro-proteins and microbial components required for the priming of NLRP3 inflammasome (202). Besides, caspase-8 in A20-deficient cells shows elevated activity and cleaves in more pro-IL-1β, suggesting a negative role of A20 in mediating caspase-8 and IL-1β production (217). Also, A20 restricts NLRP3 function through caspase1-caspase8-receptor-interacting protein kinase (RIPK1)-RIPK3 complex (217). Apart from that, A20 inhibits caspase-1-dependent pyroptosis (226). Although the underlying mechanism remains incompletely understood, this still substantiates the regulatory role of A20. In summary, A20 inhibits the production of IL-1β thereby mitigating downstream inflammatory responses and bone resorption.

**FIGURE 5** | A20 inhibits IL-1β production and downstream periodontal inflammation. (A) On microbial activation, PRRs containing CARD induces pro-IL-1β and pro-IL-18 production through NF-κB pathway. (B) NLRP 3 inflammasome is assembled by NLRP3, pro-Caspase-1 and ASC. (C) NLRP3 inflammasome is primed by microbial signals and activated by ROS, hypoxia and K⁺ efflux. (D) Mature NLRP3 inflammasome confers Caspase-1 with bioactivity. (E) Caspase-1 cleaves and activates pro-IL-1β and pro-IL-18 that induces inflammation. (F) Caspase-1 also cleaves GSDMD whose active N-terminus forms a pore on the cellular surface and causes pyroptosis. (G) A20 inhibits NF-κB signaling through IκBα. (H) A20 degrades RIPK1, impedes pro-Caspase-8 production and thus inhibits IL-1β production. (I) A20 restricts NLRP3 function through caspase1-caspase8-RIPK1-RIPK3 complex. (J) A20 inhibits caspase-1 dependent pyroptosis. PRRs, pattern recognition receptors; CARD, caspase activation and recruitment domain; NLRP3, NOD (nucleotide oligomerization domain)-, LRR (leucine-rich repeat)-, and PYD (pyrin domain)-containing protein 3; ASC, apoptosis-associated speck protein containing a CARD; ROS, reactive oxygen species; GSDMD, gasdermin D; IκBα, inhibitor of NF-κB alpha; RIPK, receptor-interacting protein kinase.
CONCLUSION

Periodontitis is a multifactorial chronic oral disease affecting a considerable proportion of the world population. Over the years, evidence has moved from minimal to substantial that periodontitis is closely related to an array of systematic diseases like diabetes, obesity, hypertension, and especially rheumatoid arthritis. Hence, superior periodontal treatments may lead to improved overall health conditions. Although modern surgical and non-surgical treatments against periodontitis have helped patients to some extent, the underlying mechanism has not been fully revealed. Here we conclude the pathogenesis of periodontitis and the essential role of Th17 cells in it. We also summarized some modulators of Th17 cells for they could be future therapeutic targets.

However, current understanding of Th17 cells and periodontitis is far from enough. For example, anti-IL-17A antibody alone could not alleviate periodontitis because of the concomitant rise in GM-CSF. Would the addition of anti-GM-CSF antibody be helpful? Also, the heterogeneity and plasticity of Th17 cells have hinted us that therapies targeting Th17 cells need revision. Does ex Th17 exhibit bioactivities that we are currently unaware of? Is it possible that we can create a cytokine milieu that converts pathogenic Th17 cells to non-pathogenic ones? These questions await further explanation.

Given the outstanding performance of A20 in restricting Th17 cells, we anticipate that A20 may be a potential target in restricting periodontal inflammation and bone resorption but there are still many open questions as to whether there are more explanations for the interplay between A20 and Th17 cell expansion. For example, the cellular mechanism through which ZnF7 motif in A20 restricts Th17 differentiation remain ill-defined and the interplay between IL-17/IL-23 axis and A20 is yet not understood and this calls for further exploration into the anfractuous immune system.

AUTHOR CONTRIBUTIONS

NH, HD, and YL wrote the manuscript. BS reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the National Natural Science Foundation of China, Grant/Award Numbers: 81972193 and 81702271; the Department of Science and Technology of Sichuan Province, Grant/Award Number: 2019YJ0041; the Scientific Research Foundation for Recruited Talents, West China Hospital of Stomatology Sichuan University, Grant/Award Number: QDIF2019-1.

REFERENCES

1. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global Burden of Severe Periodontitis in 1990-2010: A Systematic Review and Meta-Regression. *J Dent Res* (2014) 93(11):1045–53. doi: 10.1177/0022034514524941
2. He W, You M, Wan W, Xu F, Li F, Li A. Point-Of-Care Periodontitis Testing: Biomarkers, Current Technologies, and Perspectives. *Trends Biotechnol* (2018) 36(11):1127–44. doi: 10.1016/j.tibtech.2018.05.013
3. Hajishengallis G, Chavakis T, Lambris JD. Current Understanding of Periodontal Disease Pathogenesis and Targets for Host-Modulation Therapy. *Periodontol 2000* (2020) 84(1):14–34. doi: 10.1111/prd.12331
4. Teles F, Wang Y, Hajishengallis G, Hasturk H, Marchesan JT. Impact of Systemic Factors in Shaping the Periodontal Microbiome. *Periodontol 2000* (2021) 85(1):126–60. doi: 10.1111/prd.12356
5. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal Diseases. *Nat Rev Dis Primers* (2017) 3:17038. doi: 10.1038/nrdp.2017.38
6. Zheng M, Wang C, Ali A, Shih YA, Xie Q, Guo C. Prevalence of Periodontitis in People Clinically Diagnosed With Diabetes Mellitus: A Meta-Analysis of Epidemiologic Studies. *Acta Diabetol* (2021). doi: 10.1007/s00592-021-01738-2
7. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalński R, Pelka P, Nowakowski D, et al. Causal Association Between Periodontitis and Hypertension: Evidence From Mendelian Randomization and a Randomized Controlled Trial of non-Surgical Periodontal Therapy. *Eur Heart J* (2019) 40(42):3459–70. doi: 10.1093/eurheartj/ehz646
8. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juaneey JR, D’Auito F, Bouchard P, et al. Periodontitis and Cardiovascular Diseases: Consensus Report. *J Clin Periodontol* (2020) 47(3):268–88. doi: 10.1111/jcpe.13189
9. D’Auito F, Gkranias N, Bhowruth D, Khan T, Alieu A, Shiha AY, et al. Systemic Effects of Periodontitis Treatment in Patients With Type 2 Diabetes: A 12 Month, Single-Centre, Investigator-Masked, Randomised Trial. *Lancet Diabetes Endocrinol* (2018) 6(12):954–65. doi: 10.1016/s2213-8587(18)30038-x
10. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A Distinct Lineage of CD4 T Cells Regulates Tissue Inflammation by Producing Interleukin 17. *Nat Immunol* (2005) 6(11):1133–41. doi: 10.1038/ni2615
11. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, et al. The Orphan Nuclear Receptor RORgammat Directs the Differentiation Program of Proinflammatory IL-17+ T Helper Cells. *Cell* (2006) 126(6):121–33. doi: 10.1016/j.cell.2006.07.035
12. Bunte K, Beikler T. Th17 Cells and the IL-23/IL-17 Axis in the Pathogenesis of Periodontitis and Immune-Mediated Infectious Diseases. *Int J Mol Sci* (2019) 20(14):3394. doi: 10.3390/ijms20143394
13. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, et al. Development, Cytokine Profile and Function of Human Interleukin 17-Producing Helper T Cells. *Nat Immunol* (2007) 8(9):890–7. doi: 10.1038/nri2197
14. Wang D, Lei L. Interleukin-35 Regulates the Balance of Th17 and Treg Responses During the Pathogenesis of Connective Tissue Diseases. *Int J Rheum Dis* (2020) 24(1):21–7. doi: 10.1111/1756-185X.13962
15. Yang G, Xia Y, Ren W. Glutamine Metabolism in Th17/Treg Cell Fate: Applications in Th17 Cell-Associated Diseases. *Sci China Life Sci* (2020) 64(2):221–33. doi: 10.1007/s11427-020-1703-2
16. N Dutzan and L Abusleme eds. T Helper 17 Cells as Pathogenic Drivers of Periodontitis. Cham: Springer International Publishing (2019).
17. Dutzan N, Kajikawa T, Abusleme L, Greenwell-Wild T, Zuazo CE, Ikeuchi T, et al. A Dysbiotic Microbiome Triggers TH17 Cells to Mediate Oral Mucosal Immunopathology in Mice and Humans. *Sci Trans Med* (2018) 10(463):eaat0797. doi: 10.1126/scitransmed.eaat0797
18. Xiao E, Mattos M, Vieira GHA, Chen S, Correia JD, Wu Y, et al. Diabetes Enhances IL-17 Expression and Alters the Oral Microbiome to Increase Its Pathogenicity. *Cell Host Microbe* (2017) 22(1):120–6. doi: 10.1016/j.chom.2016.07.014
19. Caferera EA, Castro-Saavedra S, Fuentes-Barros G, Melgar-Rodriguez S, Rivera F, Carvajal P, et al. Boldine Inhibits the Alveolar Bone Resorption During Ligature-Induced Periodontitis by Modulating the Th17/Treg Imbalance. *J Periodontol* (2021) 92(1):123–36. doi: 10.1002/jper.20-0055
20. Caferera EA, Terraza-Aguirre C, Herrera R, Faàndez N, González N, Rojas C, et al. Interleukin-35 Inhibits Alveolar Bone Resorption by Modulating the
41. Naginyte M, Do T, Meade J, Devine DA, Marsh PD. Enrichment of T helper type 17 (Th17) cells in periodontitis. *J Clin Periodontol* (2020) 47 (6):676–88. doi: 10.1111/jcpe.13282

42. Shi T, Jin Y, Mao Y, Wang Y, Zhou Y, Lin X, IL-10 Secretory B Cells Regulate Periodontal Immune Response During Periodontitis. *Odontology* (2020) 108(3):350–7. doi: 10.1007/s10266-019-00470-2

43. Bi CS, Li X, Qu HL, Sun LJ, An Y, Hong YL, et al. Calcitriol Inhibits Osteoclastogenesis in an inflammatory Environment by Changing the Proportion and Function of T Helper Cell Subsets (Th2/Th17). *Cell Proliferation* (2020) 53(6):e12287. doi: 10.1111/cip.12827

44. Silfvast-Kaiser A, Paek SY, Menter A. Anti-IL17 Therapies for Psoriasis. Expert Opinion on Biol Ther (2019) 19(1):45–54. doi: 10.1080/17445862.2019.1555235

45. Mooney EC, Sahingur SE. The Ubiquitin System and A20: Implications in Regulation of Periodontal Immune Response During Periodontitis. *J Periodontol* (2021) 100(1):10–20. doi: 10.1017/s0022391320034514

46. Dixit VM, Green S, Sarma V, Holzman LB, Wolf FW, O’Rourke K, et al. Tumor Necrosis Factor-Alpha Induction of Novel Gene Products in Human endothelial Cells Including a Macrophage-Specific Chemotaxin. *J Biol Chem* (1990) 265(5):2973–8. doi: 10.1016/S0022-2520(18)37614-5

47. Taniguchi K, Karim M. NF-kB, Inflammation, Immunity and Cancer: Coming of Age. *Nat Rev Immunol* (2018) 18(5):309–24. doi: 10.1038/nri.2017.142

48. Garg AV, Ahmed M, Vallejo AN, MA, A, Gaffen SL. The Deubiquitinase A20 Mediates Feedback Inhibition of Interleukin-17 Receptor Signaling. *Sci Signaling* (2013) 6(278):ra44. doi: 10.1126/scisignal.2003699

49. Prémont D, van Loo G, Bertrand MMM, A20 and Cell Death-Driven Inflammation. *Trends Immunol* (2020) 41(5):421–35. doi: 10.1016/j.ti.2020.03.001

50. Polyrakis A, Martens A, Eren RO, Shirasaki Y, Yamagishi M, Yamaguchi Y, et al. A20 Prevents Inflammation-Dependent Arthritis by Inhibiting Macrophage Necroptosis Through its ZnF7 Ubiquitin-Binding Domain. *Nat Cell Biol* (2021) 19(1):45–57. doi: 10.1007/s00876-020-00895-9

51. Hugoson A, Jordan T. Frequency Distribution of Individuals Aged 20-70 Years According to Severity of Periodontal Disease. *Community Dent Oral Epidemiol* (1982) 10(4):187–92. doi: 10.1111/j.1600-0528.1982.tb00377.x

52. Bartold PM, Van Dyke TE. Host Modulation: Controlling the Infection. *Periodontol 2000* (2000) 17(1):317–39. doi: 10.1111/j.1600-0528.2000.tb00511.x

53. Van Dyke TE, Bartold PM, Reynolds EC. The Nexus Between Periodontal Inflammation and Allergy. *Front Immunol* (2020) 11:511. doi: 10.3389/fimmu.2020.00511

54. Lamont RJ, Koo H, Hajishengallis G. The Oral Microbiota: Dynamic Communities and Host Interactions. *Nat Rev Microbiol* (2018) 16 (12):745–59. doi: 10.1038/s41579-018-0089-x

55. Dutzan N, Abusleme L, Bridgeham H, Greenwell-Wild T, Zangerle-Murray T, Fife ME, et al. On-Going Mechanical Damage From Mastication Drives Homeostatic Th17 Cell Responses at the Oral Barrier. *Immunity* (2017) 46 (1):133–47. doi: 10.1016/j.immuni.2016.12.010

56. Moussopoulou NM, Konkel JE. Tissue-Specific Immunity at the Oral Mucosal Barrier. *Trends Immunol* (2018) 39(4):276–87. doi: 10.1016/j.ti.2017.08.005

57. Page RC, Schroeder HE. Pathogenesis of Inflammatory Periodontal Disease. A Summary of Current Work. *Lab Invest* (1976) 34(3):235–49.

58. Hajishengallis G. The Inflammatopic Character of the Periodontitis-Associated Microbiota. *Mol Oral Microbiol* (2014) 29(6):248–57. doi: 10.1016/j.molmic.2012.0605

59. Lamont RJ, Hajishengallis G. Polymicrobial Synergy and Dysbiosis in Inflammatory Disease. *Trends Mol Med* (2015) 21(3):172–83. doi: 10.1016/j.molmed.2014.11.004

60. Naginyte M, Do T, Meade J, Devine DA, Marsh PD. Enrichment of T helper type 17 (Th17) cells in periodontitis. *J Clin Periodontol* (2020) 47 (6):676–88. doi: 10.1111/jcpe.13282

61. Shi T, Jin Y, Mao Y, Wang Y, Zhou Y, Lin X, IL-10 Secretory B Cells Regulate Periodontal Immune Response During Periodontitis. *Odontology* (2020) 108(3):350–7. doi: 10.1007/s10266-019-00470-2

62. Bi CS, Li X, Qu HL, Sun LJ, An Y, Hong YL, et al. Calcitriol Inhibits Osteoclastogenesis in an inflammatory Environment by Changing the Proportion and Function of T Helper Cell Subsets (Th2/Th17). *Cell Proliferation* (2020) 53(6):e12287. doi: 10.1111/cip.12827
Huang et al. Th17 Cells in Periodontitis

Gingival Expressions of Interleukin-17 and Retinoic Acid Receptor-Related Orphan Receptor \( \gamma \) and Alveolar Bone Loss in Experimental Periodontitis. J Periodontol (2016) 87(11):e183–91. doi: 10.1902/jp.2016.150722

83. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annu Rev Immunol (2009) 27:485–517. doi: 10.1146/annurev.immunol.021908.132710

84. Codarri L, Gyüve\'zsi V, Tosevski V, Hesske L, Fontana A, Magne\'net I, et al. Ror\( \gamma \) Drives Production of the Cytokine GM-CSF in Helper T Cells, Which is Essential for the Effector Phase of Autoimmune Neuroinflammation. Nat Immunol (2011) 12(6):560–7. doi: 10.1038/ni.2027

85. Cheng WC, Hughes FJ, Taams LS. The Presence, Function and Regulation of IL-17 and Th17 Cells in Periodontitis. J Clin Periodontol (2014) 41(6):541–9. doi: 10.1111/jcpe.12238

86. Granet C, Maslin\'ski N, Mi\'ssoes P. Increased AP-1 and NF-kappaB Activation and Recruitment With the Combination of the Proinflammatory Cytokines IL-1 beta, Tumor Necrosis Factor Alpha and IL-17 in Rheumatoid Synovocytes. Arthritis Res Ther (2004) 6(3):R90–8. doi: 10.1186/ar1159

87. Shen F, Gaff\'en SL. Structure-Function Relationships in the IL-17 Receptor: Implications for Signal Transduction and Therapy. Cytokine (2008) 41(2):92–104. doi: 10.1016/j.cyt0.2007.11.013

88. Veldhoen M. Interleukin 17 is a Chief Orchestrator of Immunity. Nat Immunol (2017) 18(6):612–21. doi: 10.1038/nmi.3742

89. Acosta-Rodr\'iguez EV, Napolitani G, Lanzavecchia A, Sallusto F. Interleukins 1beta and 6 But Not Transforming Growth Factor-Beta are Essential for the Differentiation of Interleukin 17-Producing Human T Helper Cells. Nat Immunol (2007) 8(9):942–9. doi: 10.1038/nmi1496

90. Ogura H, Murakami M, Okuyama Y, Tsuruoka M, Kitabayashi C, Kanamoto M, et al. Interleukin-17 Promotes Autoimmunity by Triggering a Positive-Feedback Loop. Via Interleukin-6 Induction Immun (2008) 29(6):628–36. doi: 10.1007/s00249-008-07018

91. Qian Y, Liu C, Hartupee J, Altuntas CZ, Gulen MF, Jane-Wit D, et al. The Adaptor Act1 is Required for Interleukin 17-Dependent Signaling Associated With Autoimmune and Inflammatory Disease. Nat Immunol (2007) 8(3):247–56. doi: 10.1038/nmi.439

92. Nupet\'schinj J, Wu H. Molecular Basis of NF-\( \kappa \)b Signaling. Annu Rev Bio\( \kappa \)s (2013) 42:443–68. doi: 10.1146/annurev-bio\( \kappa \)phys-083012-130338

93. Sender SU, Saret S, Tang W, Sturdevant DE, Porcella SF, Siebenlist U. IL-17-Induced NF-kappaB Activation via CJK5/Act1: Physiologic Significance and Signaling Mechanisms. J Biol Chem (2011) 286(15):12881–90. doi: 10.1074/jbc.M110.199547

94. Ruddy MJ, Wong GC, Liu XK, Yamamoto H, Kucharro VK. Interleukin-6 Promotes NK Cell Production of Interleukin-17 During Toxoplasmosis. J Immunol (Baltimore Md: 1950) (2010) 184(4):1776–83. doi: 10.4049/jimmunol.0901843

95. Cua DJ, Tato CM. Innate IL-17-Producing Cells: The Sentinels of the Immune System. Nat Rev Immunol (2010) 10(7):479–89. doi: 10.1038/nri2800

96. Richardson JP, Moyes DL. Adaptive Immune Responses to Candida Albicans Infection. Virulence (2015) 6(4):327–37. doi: 10.4161/viru.20150595.201504977

97. Passos ST, Silver JS, O'Hara AC, Sehy D, Stumhofer JS, Hunter CA. IL-6 Promotes NK Cell Production of IL-17 During Toxoplasmosis. J Immunol (Baltimore Md: 1950) (2010) 184(4):1776–83. doi: 10.4049/jimmunol.0901843

98. Gaffen SL, Moutsopoulos NM. Regulation of Host-Microbe Interactions at Oral Mucosal Barriers by Type 17 Immunity. Sci Immunol (2020) 5(43):eaau4594. doi: 10.1126/sciimmunol.aau4594

99. Aguilar-Flores C, Castro-Escamilla O, Ortega-Rocha EM, Maldonado-Garcia C, Jurado-Santa Cruz F, Perez-Montesinos G, et al. Association of Pathogenic Th17 Cells With the Disease Severity and Its Potential Implication for Biological Treatment Selection in Psoriasis Patients. J Invest Dermatol (2020) 2020:6605147. doi: 10.1015/j.jid.2020.6605147

100. Leippe J, Grunke M, Dechant C, Reindl C, Kerzendorf U, Schulze-Koops H, et al. IL-17 in Human Autoimmune Arthritis. Arthritis Rheum (2010) 62(10):2876–85. doi: 10.1002/art.27622

101. Dutzan N, Konkel JE, Greenwell-Wild T, Moutsopoulos NM. Characterization of the Human Immune Cell Network at the Gingival Barrier. Mucosal Immunol (2016) 9(5):1163–72. doi: 10.1038/mi.2015.136

102. Adibadr M, Deyhimi P, Ganjali\'khani Hakemi M, Beharmania P, Shahabu\'ei M, Rafie\'i L. Signs of the Presence of Th17 Cells in Chronic Periodontal Disease. J Periodontal Res (2012) 47(4):525–31. doi: 10.1111/j.1600-0765.2011.01464.x

103. Yu JJ, Ruddy MJ, Wong GC, Sintesca C, Baker PJ, Smith JB, et al. An Essential Role for IL-17 in Preventing Pathogen-Initiated Bone Destruction: Recruitment of Neutrophils to Inflamed Bone Requires IL-17 Receptor-Dependent Signals. Blood (2007) 109(9):3794–802. doi: 10.1182/blood-2005-09-011016

104. Yu JJ, Ruddy MJ, Conti HR, Boonanantanasarn K, Gaffen SL. The Interleukin-17 Receptor Plays a Gender-Dependent Role in Host Protection Against Porphyrornomas Gingivalis-Induced Periodontal Bone Loss. Infect Immun (2008) 76(9):4296–13. doi: 10.1128/IAI.01209-07

105. Milher JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 Cell Differentiation in Subjects With Autosomal Dominant Hyper-IgM Syndrome. Nature (2008) 452(7188):773–6. doi: 10.1038/nature06764

106. Bakar B, Yetkin Ay Z, Buiyak\'haram H, Kumbul Dogu\'c D, Bayram D, Candan IA, et al. Effect of Curcumin on Systemic T Helper 17 Cell Response;
Through Direct, Reciprocal Actions of STAT3 and STAT5. *Nat Immunol* (2011) 12(3):247–54. doi: 10.1038/ni.1995

140. Li L, Wang J, Zhang F, Chai Y, Brand D, Wang X, et al. Role of SMAD and non-SMAD Signals in the Development of Th17 and Regulatory T Cells. *J Immunol* (Baltimore Md: 1950) (2010) 184(8):4295–306. doi: 10.4049/jimmunol.0903348

141. Massagué J. TGFβ Signalling in Context. *Nat Rev Mol Cell Biol* (2012) 13 (10):616–30. doi: 10.1038/nrm3344

142. Yoon JH, Sudo K, Kuroda M, Kato M, Lee IK, Han JS, et al. Phosphorylation Status Determines the Opposing Functions of Smad2/Smad3 as STAT3 Cofactors in TH17 Differentiation. *Nat Commun* (2015) 6:6700. doi: 10.1038/ncomms8600

143. Zhang S, Takaku M, Zou L, Gu AD, Chou WC, Zhang G, et al. Reversing SKI-SMAD4-Mediated Suppression is Essential for T(H)17 Cell Differentiation. *Nature* (2017) 551(7678):105–9. doi: 10.1038/nature22483

144. Bonncon P, Atanassoski S. C-Ski in Health and Disease. *Cell Tissue Res* (2012) 347(1):51–64. doi: 10.1007/s00411-011-1180-z

145. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, et al. Critical Diverse Targets of the Transcription Factor STAT3 Contribute to T Cell Pathogenicity and Homeostasis. *J Immunol* (2009) 30(4):576–87. doi: 10.1016/j.immuni.2009.02.007

146. Sha Y, Markovic-Plese S. Activated IL-1r1 Signaling Pathway Initiates Th17 Cell Differentiation via Interferon Regulatory Factor 4 Signaling in Patients with Relapsing-Remitting Multiple Sclerosis. *Front Immunol* (2016) 7:543. doi: 10.3389/foimm.2016.00543

147. Mailer RK, Joly AL, Liu S, Elias S, Tegner J, Andersson J. IL-1 Signaling Modulates Activation of STAT Transcription Factors to Modulate Interferon Regulatory Factor-Kappa B Ligand, Interleukin (IL) -17, IL-10 and Transforming Growth Factor-Beta During the Progression of Chronic Periodontitis. *J Clin Periodontol* (2009) 36(5):396–403. doi: 10.1111/j.1600-051X.2009.01390.x

148. Alvarez C, Suliman S, Almarhoumi R, Vega ME, Rojas C, Monasterio G, et al. Regulatory T Cell Phenotype and Anti-Osteoclastogenic Function in Experimental Periodontitis. *Sci Rep* (2020) 10(1):19018. doi: 10.1038/s41598-020-76038-w

149. He J, Zhang X, Wei Y, Sun X, Chen Y, Deng J, et al. Low-Dose Interleukin-2 Treatment Selectively Modulates CD4(+) T Cell Subsets in Patients With Systemic Lupus Erythematosus. *Nat Med* (2016) 22(9):991–3. doi: 10.1038/nm.4148

150. Dey I, Bisahy R. Impact of Simultaneous Neutralization of IL-17A and Treatment With Recombinant IL-2 on Th17-Treg Cell Population in Seraeus Induced Septic Arthritis. *Microb Pathog* (2020) 139:103903. doi: 10.1016/j.micpath.2019.103903

151. Yu CR, Oh HM, Goelstaneh N, Amadi-Obi A, Lee YS, Eseonu A, et al. Persistence of IL-2 Expressing Th17 Cells in Healthy Humans and Experimental Autoimmune Uveitis. *Eur J Immunol* (2011) 41(12):3495–505. doi: 10.1002/eji.201141654

152. Aschenbrenner D, Foglierini M, Jarrossay D, Hu D, Weiner HL, Kuchroo VK, et al. An Immunoregulatory and Tissue-Residence Program Modulated by C-MAF in Human TH17 Cells. *Nat Immunol* (2018) 19(10):1126–36. doi: 10.1038/s41590-018-0274-9

153. Mazzoni A, Maggi L, Liotta F, Cosmi L, Annunziato F, Biolonti F, and Annunziato F. Biological and Clinical Significance of T Helper 17 Cell Plasticity. *Immunity* (2015) 48(4):287–95. doi: 10.1016/j.immuni.13124

154. Lee PW, Yang R, Racke MK, Lovett-Racke AE. Analysis of TGF-β1 and TGF-β3 as Regulators of Eosinophilic Th17 Cells: Implications for Multiple Sclerosis. *Brain Behav Immun* (2015) 46:44–9. doi: 10.1016/j.bbi.2014.12.007

155. McGrechy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschien W, McClanahan T, et al. TGF-β and IL-6 Drive the Production of IL-17 and IL-10 by T Cells and Restrains Th(H)-17 Cell-Mediated Pathology. *Nat Immunol* (2007) 8(12):1390–7. doi: 10.1038/nl539

156. Lee Y, Awasthi A, Yosef N, Quintana FJ, Xiao S, Peters A, et al. Induction and Molecular Signature of Pathogenic Th17 Cells. *Nat Immunol* (2012) 13 (10):991–9. doi: 10.1038/nl2416

157. Gaulton P, Jellert T, Yosef N, Lee Y, Gertner Rona S, Yang Li V, Wu C, et al. Single-Cell Genomics Unveils Critical Regulators of Th17 Cell Pathogenicity. *Cell* (2015) 163(6):1400–12. doi: 10.1016/j.cell.2015.11.009

158. Papp KA, Leonard C, Menter A, Ortonne JP, Krueger JG, Kricorian G, et al. Bridalveil, an Anti-Interleukin-17-Receptor Antibody for Psoriasis. *New Engl J Med* (2012) 366(13):1181–9. doi: 10.1056/NEJMoa1109077

159. Omenetti S, Busi C, Metjidi A, Ioseppon N, Lee S, Tolaini M, et al. The Intestine Harbors Functionally Distinct Homeostatic Tissue-Resident and Inflammatory Th17 Cells. *Immunity* (2019) 51(1):77–89.e6. doi: 10.1016/j.immuni.2019.05.004

160. Saraiva M, Christensen JR, Vmeldhoon M, Murphy TI, Murphy KM, O’Garra A. Interleukin-10 Production by Th Cells Requires Interleukin-12-Induced STAT4 Signaling and TGF-β1 as Regulators of Encephalitogenic Th17 Cells: Implications for Multiple Sclerosis. *Brain Behav Immun* (2015) 46:44–9. doi: 10.1016/j.bbi.2014.12.007

161. Amezcua Vesely MC, Ioseppon N, Maggi L, Liotta F, Cosmi L, Annunziato F. Biological and Clinical Significance of T Helper 17 Cell Plasticity. *Immunity* (2015) 48(4):287–95. doi: 10.1016/j.immuni.13124

162. Gublottomme Jellert T, Yosef N, Lee Y, Gertner Rona S, Yang Li V, Wu C, et al. Single-Cell Genomics Unveils Critical Regulators of Th17 Cell Pathogenicity. *Cell* (2015) 163(6):1400–12. doi: 10.1016/j.cell.2015.11.009
Pathogenic Interferon-γ Producing T Helper 17 Cells. *Immunity* (2014) 40 (3):355–66. doi: 10.1111/jimmun.2014.01.002

Cerboni S, Gehrmann U, Preite S, Mitra S. Cytokine-Regulated Th17 Plasticity in Human Health and Diseases. *Immunology* (2021) 163(1):3–18. doi: 10.1111/immm.13280

Maggi L, Santarlasci V, Capone M, Rossi MC, Querci V, Mazzoni A, et al. Distinctive Features of Classic and Nonclassic (Th17 Derived) Human Th1 Cells. *Eur J Immunol* (2012) 42(12):3180–8. doi: 10.1002/eji.201242648

Bittner-Eddy PD, Fischer LA, Costalanga M. Transient Expression of IL-17A in Foxp3 Fate-Tracking Cells in Porphyromonas Gingivalis-Mediated Oral Dysbiosis. *Front Immunol* (2020) 11:677. doi: 10.3389/fimmu.2020.00677

Zwicky P, Unger S, Becher B. Targeting Interleukin-17 in Chronic Inflammatory Disease: A Clinical Perspective. *J Exp Med* (2020) 217(1): e20191123. doi: 10.1084/jem.20191123

Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A Prospective Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Brodalumab in Patients With Moderate-to-Severe Plaque Psoriasis. *Br J Dermatol* (2016) 175(2):273–86. doi: 10.1111/bjd.14493

Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and Pathologic Significances in Increase in Serum Interleukin-6 (IL-6) and Soluble IL-6 Receptor After Administration of an Anti-IL-6 Receptor Antibody, Tocilizumab, in Patients With Rheumatoid Arthritis and Castleman Disease. *Blood* (2008) 112(10):3959–64. doi: 10.1182/blood-2008-05-155846

Kobayashi T, Okada M, Ito S, Kobayashi D, Ishida K, Kojima A, et al. Restraint of NF-κB Activity Through Ubiquitin Binding to A20 in Foxp3+ Tregs by Its Unique Ubiquitin Binding Domain. *Immunity* (2011) 34(2):206–16. doi: 10.1016/j.immuni.2011.01.002

Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Their Regulation in Periodontal Disease: A Review. *J Periodontal Res* (2012) 51(5):498. doi: 10.1111/jre.12332

Bosanac I, Wertz IE, Pan B, Yu C, Kusam S, Lam C, et al. Ubiquitin Binding to A20 Zoophilic Is Required for Modulation of NF-κb Signaling. *Mol Cell* (2010) 40(4):548–57. doi: 10.1016/j.molcel.2010.10.009

Tokunaga F, Nishimatsu H, Ishitani R, Goto E, Noguchi T, Mio K, et al. Specific Recognition of Linear Polysubiquitin by A20 Zinc Finger 7 Is Involved in NF-κb Regulation. *EMBO J* (2012) 31(19):3856–70. doi: 10.1038/emboj.2012.241

Sun SC. The non-Canonical NF-κb Pathway in Immunity and Inflammation. *Nat Rev Immunol* (2017) 17(9):545–58. doi: 10.1038/nri.2017.52

Zhang Q, Lenardo MJ, Baltimore D. 30 Years of NF-κb: A Blossoming of Relevance to Human Pathobiology. *Cell* (2017) 168(1–2):37–57. doi: 10.1016/j.cell.2016.12.012

Skaug B, Chen J, Du H, He J, Ma A, Chen ZJ. Direct, Noncatalytic Mechanism of IKK Inhibition by A20. *Mol Cell* (2011) 44(4):559–71. doi: 10.1016/j.molcel.2011.09.015

Chen ZJ. Ubiquitination in Signaling to and Activation of IKK. *Immunol Rev* (2012) 246(1):95–106. doi: 10.1111/j.1600-065X.2012.01080.x

Wertz IE, O’Rourke KM, Zhou H, Eby M, Aravidin L, Seshagiri S, et al. De-Ubiquitination and Ubiquitin Ligase Domains of A20 Downregulate NF-kappaB Signalling. *Nature* (2004) 430(7000):694–9. doi: 10.1038/nature02794

Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23–IL-17 Immune Axis: From Mechanisms to Therapeutic Testing. *Nat Rev Immunol* (2014) 14(9):585–600. doi: 10.1038/nri3707

Feng Z, Zhai Y, Zheng Z, Yang L, Luo X, Dong X, et al. Loss of A20 in BM-MSCs Regulates the Th17/Treg Balance in Rheumatoid Arthritis. *Sci Rep* (2018) 8(1):427. doi: 10.1038/s41598-017-18693-0

Razani B, Whang MI, Kim FS, Nakamura MC, Sun X, Advincula R, et al. Non-Canonical Ubiquitin Binding by A20 Prevents Psoriatic Arthritis-Like Disease and Inflammation. *Nat Immunol* (2020) 21(4):422–33. doi: 10.1038/s41590-020-0634-4

Shao TY, Ang WXG, Jiang TT, Huang FS, Andersen H, Kinder JM, et al. Commensal Candida Albicans Positively Calibrates Systemic Th17 Immunological Responses. *Cell Host Microbe* (2019) 25(3):404–17.e6. doi: 10.1016/j.chom.2019.02.004

Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of Intestinal Th17 Cells by Segmented Filamentous Bacteria. *Cell* (2009) 139(3):485–98. doi: 10.1016/j.cell.2009.09.033

Brembilla NC, Senra L, Boehncke WH. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. *Front Immunol* (2018) 9:1682. doi: 10.3389/fimmu.2018.01682

McGrath MJ, Cua DJ, Gaffen SL. The IL-17 Family of Cytokines in Health and Disease. *Immunity* (2019) 50(4):892–906. doi: 10.1016/j.immuni.2019.03.021

Martens A, van Loo G. A20 at the Crossroads of Cell Death, Inflammation, and Autoimmunity. *Cold Spring Harbor Perspect Biol* (2019) 11(2):a036418. doi: 10.1101/cshperspect.a036418

Ho AW, Garg AV, Monin L, Simpson-Abelson MR, Kinner L, Gaffen SL. The Anapase-Processive Complex Protein 5 (Anap5C) Associates With A20 and Inhibits IL-17-Mediated Signal Transduction. *PloS One* (2013) 8(7):e70168. doi: 10.1371/journal.pone.0070168

Hirota K, Yoshitomi H, Hashimoto M, Maeda S, Teradaira S, Sugimoto N, et al. Preferential Recruitment of CCR6-Expressing Th17 Cells to Inflamed Joints. *Vita CCL20 Rheumatoid Arthritis Anim Model J Exp Med* (2007) 204(12):2803–12. doi: 10.1084/jem.20071397

Zheng R, Wu Z, Li M, Shao M, Hu T. Interleukin-1β is a Potential Therapeutic Target for Periodontitis: A Narrative Review. *Int J Oral Sci* (2020) 12(1):2. doi: 10.1038/s41368-019-0068-8

Aral K, Milward MR, Kapila Y, Berdeli A, Cooper PR. Inflammases and Their Regulation in Periodontal Disease: A Review. *J Periodontal Res* (2020) 55(4):473–87. doi: 10.1111/jper.12733

Yu C, Zhang C, Kuang Z, Zheng Q. The Role of NLRP3 Inflammasome Activities in Bone Diseases and Vascular Calcification. *Inflammation* (2021) 44(2):434–49. doi: 10.1007/s10573-020-01357-z

Graves DT, Cochran D. The Contribution of Interleukin-1 and Tumor Necrosis Factor to Periodontal Tissue Destruction. *J Periodontol* (2003) 74(3):391–401. doi: 10.1902/jop.2003.74.3.391
217. Duong BH, Onizawa M, Oses-Prieto JA, Advincula R, Burlingame A, Malynn BA, et al. A20 Restricts Ubiquitination of Pro-Interleukin-1β Protein Complexes and Suppresses NLRP3 Inflammasome Activity. *Immunity* (2015) 42(1):55–67. doi: 10.1016/j.immuni.2014.12.031

218. Martinon F, Burns K, Tschopp J. The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL-1β. *Mol Cell* (2002) 10(2):417–26. doi: 10.1016/s1097-2765(02)00599-3

219. He Y, Hara H, Núñez G. Mechanism and Regulation of NLRP3 Inflammasome Activation. *Trends Biochem Sci* (2016) 41(12):1012–21. doi: 10.1016/j.tibs.2016.09.002

220. Swanson KV, Deng M, Ting JP. The NLRP3 Inflammasome: Molecular Activation and Regulation to Therapeutics. *Nat Rev Immunol* (2019) 19(8):477–89. doi: 10.1038/s41577-019-0165-0

221. Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S. The P2X7 Receptor in Infection and Inflammation. *Immunity* (2017) 47(1):15–31. doi: 10.1016/j.immuni.2017.06.020

222. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 Forms an IL-1βa-Processing Inflammasome With Increased Activity in Muckle-Wells Autoinflammatory Disorder. *Immunity* (2004) 20(3):319–25. doi: 10.1016/s1074-7613(04)00046-9

223. He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, et al. Gasdermin D is an Executor of Pyroptosis and Required for Interleukin-1β Secretion. *Cell Res* (2015) 25(12):1285–98. doi: 10.1038/cr.2015.139

224. Chen Y, Yang Q, Lv C, Chen Y, Zhao W, Li W, et al. NLRP3 Regulates Abecular Bone Loss in Ligature-Induced Periodontitis by Promoting Osteoclastic Differentiation. *Cell Proliferation* (2021) 54(2):e12973. doi: 10.1111/cpr.12973

225. Isaza-Guzmán DM, Medina-Piedrahita VM, Gutiérrez-Henao C, Tobón-Arroyave SL. Salivary Levels of NLRP3 Inflammasome-Related Proteins as Potential Biomarkers of Periodontal Clinical Status. *J Periodontol* (2017) 88(12):1329–38. doi: 10.1902/jop.2017.170244

226. Vande Walle L, Van Opdenbosch N, Jacques P, Fossoul A, Verheugen E, Vogel P, et al. Negative Regulation of the NLRP3 Inflammasome by A20 Protects Against Arthritis. *Nature* (2014) 512(7512):69–73. doi: 10.1038/nature13322

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Huang, Dong, Luo and Shao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.