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# IL-17; overview and role in oral immunity and microbiome

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## Introduction

Interleukin-17 (IL-17) is a multifaceted cytokine with diverse roles both in immune-protection and also immunopathology. IL-17 has a well-recognized role in immune surveillance at mucosal and barrier surfaces (Miossec & Kolls, 2012, Song et al., 2016) but also has been increasingly implicated as a driver of immunopathology in settings of autoimmunity and chronic inflammation (Gaffen et al., 2014). The current review introduces basic aspects of IL-17 biology and examines the protective and pathogenic roles of IL-17 with a focus on oral mucosal immunity and inflammation. Specific emphasis is given to the role of the IL-17 response as a catalyst in “shaping the microbiome at the oral barrier”.

## IL-17 cytokine and its signaling

IL-17 is formally called ‘IL-17A’, but is usually referred to as IL-17 since it was the first described member of the IL-17 family (Rouvier et al., 1993). To date, the IL-17 family includes six members (from IL-17A to IL-17F) that share sequence homology (Patel & Kuchroo, 2015). IL-17A and IL-17F exhibit high sequence similarity and can form homodimers and heterodimers to signal (Miossec & Kolls, 2012). In fact, IL-17A and IL-17F signal through the same receptor complex (known as ‘IL-17R’, an heterodimer of IL-17RA and IL-17RC subunits) (Toy et al., 2006) and largely share biological functions (Miossec & Kolls, 2012). The IL-17 receptor family has additional members namely IL-17 RB, IL-17RC, IL-17RD and IL-17RE. All IL-17 receptor subunits are structurally similar, consisting of an outer membrane fibronectin III-like domain, a conserved cytoplasmic SEF/IL-17R (SEFIR) domain and a distal activation domain (CBAD) (Gaffen et al., 2014). The SEFIR domain exhibits sequence homology with the Toll/IL-1R domain (Novatchkova et al., 2003), suggesting commonalities between IL-17 and TLR signaling cascades. Engagement of IL-17 (IL-17A, IL-17F and IL-17A/F) to the IL-17R heterodimeric complex, leads to the association of the adaptor protein Act1 (previously named CIKS) through the SEFIR domain (Qian et al., 2007). Act1 recruits the TNFR-associated factor (TRAF) 6 that is poly-ubiquitinated by Act1 via its E3 ligase activity (Liu et al., 2009), triggering the activation of the canonical nuclear factor κB (NF-κB) pathway and some components of the mitogen-activated protein kinase (MAPK) pathways, namely JUN N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and p38 (Sonder et al., 2011, Patel et al., 2007).

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Additionally, IL-17 signaling can activate members of the CCAAT/enhancer-binding protein (C/EBP) family of transcription factors that are critical for the expression of certain target genes (Patel et al., 2007). mRNA stabilization events are also involved in the regulation of the IL-17 signaling pathway. Important for mRNA stabilization is the formation of the TRAF2/TRAF5 complex and recruitment of HuR and ASF/SF2, which stabilize mRNA transcript targets (Datta et al., 2010, Sun et al., 2011, Herjan et al., 2013) (Figure 1). Moreover, there are other regulators of IL-17 signaling pathway that act at different levels. The adaptor protein TRAF3 has the ability to inhibit the association of the IL-17R with Act1 and TRAF4 interferes with the Act1 and TRAF6 interaction, inhibiting downstream signal transduction (Zhu et al., 2010, Zepp et al., 2012). Act1 is stabilized by the chaperone Hsp90 that prevents its targeting for proteasomal degradation by the negative regulator βTrCP E3 ligase complex (Wang et al., 2013, Wu et al., 2014). Deubiquitinating enzymes (DUB) are also important negative regulators of this pathway. The DUB A20 removes ubiquitination residues on TRAF6 suppressing activation of NF-κB and MAPK signaling; likewise, the DUB USP25 negatively regulates IL-17 signaling by targeting both TRAF5 and TRAF6 (Song & Qian, 2013). MicroRNAs (miRNAs) have also been implicated as negative regulators of IL-17, miR-23b targets the kinases TAB2, TAB3 and IKKα, all of which are integral to the NF-κB pathway (Zhu et al., 2012). Additionally, the distal activator domain (CBAD) of the IL-17RA subunit participates on inhibitory events for IL-17 signaling, such as coordinating phosphorylation of C/EBPβ and associating with the DUB A20 (Garg et al., 2013). Lastly, it has been recently shown that the signaling molecule MCPIP1 (also known as Regnase-1), acts as a negative regulator of IL-17-induced genes, degrading mRNA of cytokines (*Il6*) and promoters needed for other gene targets (Garg et al., 2015).

In sum, the IL-17 signaling cascade is complex, involving multiple pathways and levels of regulation that continue to be interrogated expanding knowledge in the IL-17 field.

## Cellular sources of IL-17

IL-17 is primarily secreted by a distinct $CD4^+$ T cell subset, known as T helper 17 cells (Th17), named after their signature cytokine (Harrington et al., 2005). Th17 cells in different contexts can also produce other cytokines such as IL-17F, IL-21, IL-22 and granulocyte-macrophage colony-stimulating factor (GM-CSF), at varying expression levels (Liang et al., 2006, Korn et al., 2007, Codarri et al., 2011). Typically, the differentiation of naïve $CD4^+$ T cells towards an effector subset necessitates antigen engagement through the T cell receptor (TCR) and depends on the surrounding cytokine milieu. Differentiation of murine Th17 cells has been shown to be dependent on transforming growth factor β (TGF-β) and IL-6 (Veldhoen et al., 2006, Bettelli et al., 2006, Mangan et al., 2006), whereas human Th17 cells can be induced in the presence of TGF-β/IL-1β, IL-6 and IL-23 (Acosta-Rodriguez et al., 2007a, Manel et al., 2008, Volpe et al., 2008). However, human and murine Th17 cells have also been shown to be generated independent of TGF-β (Ghoreschi et al., 2010), suggesting that presence or absence of TGF-β during differentiation may determine distinct functional profiles of Th17 cells (Acosta-Rodriguez et al., 2007a, Volpe et al., 2008). IL-21 also has the ability to drive Th17 differentiation in conjunction with TGF-β (Korn et al., 2007), and is proposed as an amplification signal for differentiation since IL-21 production from Th17 cells leads to increased IL-23R expression. This is important because IL-23 is critical for

stabilization and maintenance of the Th17 phenotype and IL-23R is not typically expressed on naïve T cells. (Bettelli et al., 2008) (Burkett et al., 2015).

A critical step in the differentiation of Th17 cells is the activation of the signal transducer and activator of transcription 3 (STAT3) (Yang et al., 2007). Upon binding of the Type I cytokines IL-6, IL-21 and IL-23 to their receptors, Janus kinases (Jaks) phosphorylate the receptors, leading to the recruitment and phosphorylation of STAT3, which dimerizes and then translocates to the nucleus to enhance the expression of target genes (O'Shea et al., 2009). Then, STAT3 induces the expression of the transcription factor orphan nuclear receptor ROR-γt, which is recognized as the Th17 lineage-specific master regulator (Ivanov et al., 2006). Transcription factors BAFT and IRF4 cooperate with STAT3 to initiate the Th17 differentiation program (Ciofani et al., 2012). High throughput transcriptional network analyses have revealed that Th17 cell development is tightly controlled by 22 genes that act as positive regulators and a module of 5 genes that are negative regulators of differentiation, illustrating the complexity of the Th17 cell developmental program (Yosef et al., 2013).

After differentiation, Th17 cells are able to produce type 17 cytokines and express the CC chemokine receptor 6 (CCR-6), which allows for their preferential migration into mucosal and barrier sites (Hirota et al., 2007, Acosta-Rodriguez et al., 2007b).

Apart from Th17 cells, IL-17 is produced by other cellular sources that include γδ T cells, lymphoid tissue inducer cells (LTi), innate lymphoid cells type 3 (ILC3s) and natural killer cells (NK) (Patel & Kuchroo, 2015, Artis & Spits, 2015) (Figure 2). Particular disease settings appear to provide favorable conditions for other immune cells to produce IL-17, such as neutrophils during fungal infections and breast cancer metastasis (Taylor et al., 2014, Coffelt et al., 2015) and alveolar macrophages during allergic lung inflammation related to asthma (Song et al., 2008). In addition, mast cells have also been involved as relevant IL-17 producers in psoriatic skin (Lin et al., 2011, Mashiko et al., 2015) and in rheumatoid arthritis affected joints (Hueber et al., 2010), however, a recent report suggests that human mast cells rather than making IL-17 have the ability to capture and store exogenous IL-17A using a receptor-mediated exocytosis mechanism (Noordenbos et al., 2016).

## Cellular targets of IL-17

The IL-17 receptor complex has a ubiquitous expression and is present in a wide variety of tissues and cell types (Yao et al., 1995a, Haudenschild et al., 2002). The IL-17RA subunit of the receptor shows higher expression in cells of hematopoietic origin (Kuestner et al., 2007, Ishigame et al., 2009). In contrast, the IL-17RC subunit is primarily found in cells of non-hematopoietic lineage, such as mesenchymal, epithelial and endothelial cells, which constitute the main targets of IL-17 (Kuestner et al., 2007, Ge & You, 2008, Ishigame et al., 2009). Interestingly, macrophages seem to constitute an exception, bearing both IL-17RA and IL-17RC (Ishigame et al., 2009).

IL-17 signaling on epithelial cells is critical for physiologic regulation of mucosal immunity and barrier defenses (discussed in detail below). Additionally, in settings of inflammation IL-17 has been shown to exert its activity on a variety of cell types including keratinocytes,

fibroblasts, osteoblasts, endothelial and immune cells (Figure 2). For instance, IL-17 stimulates the production of pro-inflammatory mediators such as IL-6, IL-8, Prostaglandin E2 ($PGE_2$) and GM-CSF from epithelial, endothelial and fibroblastic cells (Yao et al., 1995b, Fossiez et al., 1996). In the context of rheumatoid arthritis (RA) IL-17 has been shown to mediate tissue pathology by acting on a variety of cell targets. IL-17 can induce the release of connective tissue destructive enzymes matrix metalloproteinase 1 (MMP-1) and MMP-3 (van Hamburg et al., 2011) from synovial fibroblasts. IL-17 is also shown to directly act on osteoblasts through different mechanisms. It can stimulate the release of $PGE_2$ followed by osteoclast differentiation factor (ODF), which induces osteoclast maturation and further bone destruction in RA (Kotake et al., 1999). In addition, IL-17 can enhance RANKL expression on osteoblasts and activate RANK signaling on osteoclasts, promoting osteoclastogenesis (Miossec & Kolls, 2012). Lastly, macrophages are reported to increase their production of the pro-inflammatory cytokines IL-1β and TNF-α upon IL-17 stimulation, further amplifying inflammatory responses (Jovanovic et al., 1998, Mosser & Edwards, 2008).

In the context of fungal infection, it has been shown that endogenous and/or exogenous IL-17 can directly enhance reactive oxygen species (ROS) production in neutrophils (Taylor et al., 2014). However, this is controversial since it has been reported previously that neutrophils do not exhibit the IL-17RC on their surface (Pelletier et al., 2010). IL-17 is also shown to play a role in the development of NK cells, which during fungal infections increase GM-CSF expression in an IL-17RA dependent manner (Bar et al., 2014).

Interestingly, IL-17 signaling can also affect T and B cell differentiation and functions. IL-17 modulates T helper cell differentiation, by inhibiting the transcription factors T-bet and STAT-1 (O'Connor et al., 2009). On autoreactive B cells, IL-17 has been documented to modulate chemotaxis and positively impacts their survival and proliferation (Xie et al., 2010).

## IL-17 as a key Mediator of Mucosal Surveillance and Barrier Integrity

IL-17 producing cells are considered by many the sentinels of mucosal barrier immunity (Cua & Tato, 2010). In fact, IL-17 exerts its function as a protective mediator in barrier immunity by multiple mechanisms. To date it is recognized that: 1) IL-17 has key roles in maintaining barrier integrity, 2) IL-17 promotes the production of antimicrobial factors which are key for the containment of pathogens and commensals at barrier sites, 3) innate cells producing IL-17 are a first line of defense strategically positioned at barrier sites to regulate the recruitment and generation of neutrophils (Figure 3).

IL-17 promotes epithelial integrity by regulating tight junction proteins that connect and stabilize epithelial cell connections with the purpose of maintaining the barrier and keeping out gut luminal contents and commensal organisms. To date it's been shown that IL-17 regulates the production of the tight junction protein claudin (Karp et al., 2010) and that IL-17A-dependent regulation of the tight junction protein occludin during epithelial injury is key in limiting excessive permeability and maintaining barrier integrity (Lee et al., 2015).

Accordingly, IL-17A or IL-17RA inhibition has been associated with severe weakening of the intestinal epithelial barrier (Maxwell et al., 2015).

Another mechanism by which IL-17 contributes to mucosal immune surveillance is the induction of antimicrobial mediators. IL-17 alone and in coordination with IL-22 induces the production of β-defensins (HBD), regenerating (ReG) proteins, S100 proteins, cathelicidins, lipocalins and lactoferrins (Liang et al., 2006, Kolls et al., 2008, Peric et al., 2008). These microbicidal agents are predominantly produced by epithelial cells. IL-17 also promotes epithelial cell secretion of chemokines such as CC-chemokine ligand 20 (CCL-20) for recruitment of neutrophils when the mucosal barrier is breached.

In fact, neutrophil recruitment is a major IL-17 function. For this, innate IL-17-producing cells are strategically positioned at barrier sites to sense injury and infection and rapidly recruit neutrophils for initial containment of any insult. This early IL-17 production is required for optimal neutrophil recruitment and resistance to infection. It is important to note that innate cells IL-17 populations not only interact with pathogens during infection, but also are critical under physiologic conditions for the containment of commensal flora and the maintenance of mucosal homeostasis (Cua & Tato, 2010). IL-17 exerts its neutrophil stimulatory functions by inducing epithelial cell secretion of granulopoietic factors such as G-CSF, GM-CSF and chemokines such as CXCL-1, 2, 5, which promote neutrophil chemotaxis (Mantovani et al., 2011)

These immune-protective functions of IL-17 have been shown to be particularly important for the clearance of specific extracellular pathogens and fungi at barrier sites. Specifically, disruptions in IL-17 signaling or production have been linked to susceptibility to *Staphylococcus aureus*, *Citrobacter rodentium* and *Klebsiella pneumoniae*, which infect the skin, colon and lung, respectively (Ishigame et al., 2009, Cho et al., 2010, Aujla et al., 2008). IL-17 immunity undoubtedly has emerged as a critical component in mucosal fungal surveillance (Lionakis et al., 2014). In both humans and animal models disruptions in the IL-17 pathway have been linked to increased susceptibility to oral and mucocutaneous candida infections (CMC) (Cypowyj et al., 2012). CMC is a disease characterized by recurrent symptomatic infections of the nails, skin, genital and oral mucosa caused by members of the genus *Candida*, mostly due to the commensal *Candida albicans* (Puel et al., 2012). *Candida albicans* does not cause chronic infections in healthy subjects; nonetheless, in immunocompromised patients might trigger a variety of distinct disease forms, with systemic and/or mucosal involvement (Cypowyj et al., 2012).

Humans with disruptions in the development of Th17 cells do exhibit susceptibility to select bacterial and fungal infections. Specifically, patients with hyper-IgE syndrome have a defect in the differentiation of Th17 cells due to a mutation in the *STAT3* gene (Milner et al., 2008) and are susceptible to skin *S. aureus* infections and recurrent pneumonias, most commonly due to *S. aureus,* but also *Streptococcus pneumoniae* and *Haemophilus influenza* infections. Lung infections with *Aspergillus* are also seen secondary to bronchiectasis. Mucocutaneous candidiasis is detected in the majority of patients (Freeman & Holland, 2009). Patients with other genetic disruptions in the IL-17 cascade or response all also present with mucocutaneous and oral candidiasis (see below).

## IL-17 as a driver of Inflammation/Immunopathology/Autoimmunity

### Evidence from human disease and disease models

IL-17 secreting cells have been documented in inflammatory lesions of patients with a variety of human inflammatory and autoimmune diseases including psoriasis, inflammatory bowel disease, rheumatoid arthritis, type 1 diabetes, multiple sclerosis and periodontitis (Gaffen et al., 2014) (Zenobia & Hajishengallis, 2015) and speculated and/or shown to be involved in the pathogenesis of the respective diseases. The link between over-activated IL-17 related responses and various inflammatory and autoimmune diseases in humans is also supported by results from genome wide association studies (GWAS) studies revealing IL-23R polymorphisms being linked with susceptibility to autoimmune diseases such as psoriasis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis and Crohn's disease (Duerr et al., 2006, Wellcome Trust Case Control et al., 2007, Liu et al., 2008) (Figure 4).

Consistent with human observations, mice deficient in IL-17A/F and related cytokines and mediators (including IL-22-, IL-23A- or IL-23RA-deficient mice) or treated with antibodies against IL-17/23 have increased susceptibility to EAE, collagen antibody-induced arthritis, and CIA, and models of inflammatory bowel disease (IBD), ankylosing spondylitis and psoriasis (Murphy et al., 2003, Langrish et al., 2005, Hue et al., 2006, van der Fits et al., 2009, Sherlock et al., 2012). On the basis of these human observations and genetic linkage studies as well as preclinical models, IL-17-specific and IL-23-specific antibody treatments have emerged as candidate therapeutic targets for Crohn's disease, psoriasis and psoriatic arthritis. Specifically, to date Secukinumab the human IL-17 antagonist has been FDA approved for the treatment of psoriatic arthritis, ankylosing spondylitis and plaque psoriasis (Langley et al., 2014). Ustekinumab inhibitor of the p40 subunit that is shared by IL-23 and IL-12 is currently FDA approved for the treatment of psoriasis and psoriatic arthritis and has shown efficacy in the treatment of Crohn's disease (Sandborn et al., 2012).

### Pathogenic Th17 cell subsets and cooperative IL-17 signaling in inflammation

IL-17's reason for being (teleology) is however not to cause disease, it is a protective mechanism geared towards the establishment of mucosal immunity. The pathologic role of IL-17 in disease appears to be context dependent and related to the development of a subset of pathogenic IL-17 secreting cell subsets. In fact, it has been recently established that there is a pathogenic subset of Th17 cells that are increasingly capable of mediating inflammatory pathology (Figure 4). Pathogenic murine Th17 cells express a unique transcriptional signature compared to non-pathogenic Th17, which includes the elevated expression of the IL-23R (Lee et al., 2012). Importantly, IL-23R deficient cells cannot induce autoimmunity irrespective of how they are differentiated *in vitro* (Lee et al., 2012). Accumulating data support a central role for IL-23 in promoting the pathogenicity of Th17 cells by several mechanisms, including through the maintenance and stabilization of the Th17 signature gene expression program (Rorc and Il17), the induction of effector genes as well as upregulation of the Il23r expression (Gaffen et al., 2014). Amongst the currently appreciated roles of IL-23 in mediating Th17 pathogenicity is its ability to stimulate the production of endogenous TGF-β3, which will thereafter drive development of a pathogenic Th17 phenotype (Lee et al., 2012). It is also well recognized that GM-CSF, which is produced by

pathogenic Th17 is dependent on IL-1 and IL-23 and is required for pathogenicity (Codarri et al., 2011, El-Behi et al., 2011). Additionally, exposure to IL-23 diminishes the concentration of the anti-inflammatory cytokine IL-10 in developing Th17 cells, which renders these cells pathogenic (McGeachy et al., 2007). Pathogenic signaling of IL-23 through the IL-23R is thought to be STAT3 mediated with STAT3 representing a major downstream mediator of IL-23R signaling in mice and humans and implicated in the pathogenicity of Th17 cells (Burkett et al., 2015). Consistent with a critical role for STAT3 in pathogenic Th17 responses, gain of function mutation in STAT3 in humans display early onset multi-organ autoimmunity (Flanagan et al., 2014, Milner et al., 2015). However, IL-23R/STAT3 activation alone cannot explain the unique requirement for IL-23 in pathogenic Th17 cell commitment, as IL-6 is an even more potent activator of STAT3. Recently IL-6 activation of STAT3 has been shown to contribute to the pathogenicity of Th17 cells via induction of the microRNA miR-183C, which is shown to inhibit Foxo1 (a negative regulator of Th17 pathogenicity)(Ichiyama et al., 2016). However, additional transcriptional regulators or signaling pathways may be operating to promote inflammatory Th17 cell effector function in different settings.

The ability of IL-17 to signal cooperatively with other cytokines is probably one of the most important aspects of its biology as it relates to disease. Importantly, on their own, IL-17A (and IL-17F) are modest activators of signaling, but they function cooperatively with other pro-inflammatory molecules, particularly TNF, but also IFNγ, IL-22, lymphotoxin, IL-1β and lipopolysaccharide (Gaffen, 2009). The molecular basis for this synergy is not completely understood and probably involves multiple mechanisms (Gaffen, 2009). In synovial tissue, IL-17 upregulates TNFR2 expression, and thereby enhances responsiveness to TNF (Zrioual et al., 2009). For some genes, cooperation between IL-17 and TNF occurs at the level of the promoter (for example, Il6 and Lcn2) and/or mRNA stability (for example, mRNA encoding chemokines such as CXCL1) (Shen & Gaffen, 2008). IL-17 also upregulates the expression of NF-κB inhibitor-ζ (IκBζ) — which promotes the expression of select target genes (Karlsen et al., 2010).

## IL-17 in oral mucosal immunity and inflammatory disease (periodontitis)

Importantly the IL-17 cytokine has been shown to play a major role both in mucosal surveillance and immunopathology at the oral mucosal barrier. Consistent with its immunoprotective role towards fungi, IL-17 is critical for oral mucosal protection against *Candida albicans.*

The Th17 lineage, acting largely through IL-17, has been elegantly shown in animal model systems to confer a dominant protective response to oral candidiasis through neutrophil recruitment and induction of antimicrobial factors (Conti et al., 2009). Consistent with experimental data HIES patients (bearing a *STAT3* mutation and defects in Th17 differentiation) exhibit great susceptibility to oral candidiasis (thrush) which has been attributed to low levels of salivary AMPs, including HBD-2 and various histatins and reduced candidacidal activity of patient saliva (Conti et al., 2011).

Similarly, patients harboring mutations in molecules required for IL-17 signaling, such as *IL-17RA, IL-17RC, IL-17F* and the adaptor protein *ACT1* also exhibit increased susceptibility to mucocutaneous, including oral, candidiasis (Puel et al., 2011, Boisson et al., 2013, Ling et al., 2015). Additional primary immunodeficiencies (PIDs) that may affect Th17 differentiation, such as gain-of-function mutations in *STAT1,* also manifest with CMC, reinforcing the importance of Th17 cells in coordinating fungal mucosal immunity (Zhang et al., 2009, Liu et al., 2011). Of the PIDs that affect fungal recognition molecules, mutations on *DECTIN-1* and its adaptor *CARD9* have been linked to defects in mounting effective IL-17 responses and CMC susceptibility (Glocker et al., 2009, Ferwerda et al., 2009). Additionally, individuals harboring genetic mutations in *AIRE* (and high titers of neutralizing autoantibodies to IL-17A, IL-17F and IL-22), almost invariably present with CMC and oral thrush (Meloni et al., 2012, Ferre et al., 2016), and show diminished *Candida* killing activity in saliva and decreased levels of the salivary AMP cystatin SA1 (Lindh et al., 2013). Finally, some of the patients with severe combined immunodeficiency (SCID) may also present with CMC, depending on their mutation and whether it affects the T lymphocytic lineage (Lionakis et al., 2014). Importantly, this continuously growing knowledge gained from the study of PIDs is helping define the role of IL-17 in human immunity (Table).

Conversely, exaggerated IL-17 responses have been linked to immunopathology, particularly periodontitis in the oral cavity. Several studies have found high levels of IL-17 in chronic periodontitis (reviewed in (Zenobia & Hajishengallis, 2015)), and indicate a correlation of increased IL-17 expression with disease severity and with clinical parameters of periodontal destruction (Johnson et al., 2004, Lester et al., 2007, Dutzan et al., 2012). In fact, IL-17 expression is higher in periodontitis than in gingivitis and is almost undetectable in healthy control tissues (Honda et al., 2008, Okui et al., 2012, Moutsopoulos et al., 2012). IL-17 is also shown to be increased in aggressive periodontitis compared to chronic periodontitis and controls (Shaker & Ghallab, 2012). Finally, numerous studies have found an increase in Th17-related cytokines in periodontal lesions, such as IL-23, IL-21 and other pro-inflammatory and osteoclastogenic mediators such as IL-6 and RANKL, respectively (Lester et al., 2007, Cardoso et al., 2009, Dutzan et al., 2009, Ohyama et al., 2009, Allam et al., 2011). In humans, the presence of Th17 cells has been previously shown in periodontal lesions (Cardoso et al., 2009) and recently Th17 cells have been identified as the main source of IL-17 in periodontitis (Dutzan et al., 2016).

Critically, tissue neutrophils are now recognized as key cellular regulators of Th17 responses in periodontitis. Studies from our group and collaborators have demonstrated that the lack or severe reduction in tissue neutrophils in patients with Leukocyte Adhesion Deficiency Type 1 (LAD-1) and relevant animal models is linked to exaggerated IL-17 responses (Moutsopoulos et al., 2014). Conversely, over-abundance of tissue neutrophils in patients with chronic and aggressive periodontitis is also linked to excessive IL-17 responses (as discussed above). Consistent with these observations, mechanistic evidence from animal models also supports that excessive neutrophil recruitment can lead to exaggerated IL-17 responses. In fact, unregulated neutrophil recruitment in the absence of Del-1 (an endogenous inhibitor of neutrophil extravasation) leads to a deregulation of the IL-17

response (Eskan et al., 2012). Collectively, all of this evidence suggests that a balance of tissue neutrophils is key in IL-17 regulation.

Dysregulated IL-17 production could be playing a pathogenic role in periodontitis though distinct but possibly overlapping mechanisms. IL-17 has the ability to amplify inflammation through excessive neutrophil recruitment, by enhancing pro-inflammatory cytokine production and by activating osteoclasts, all of which could contribute to immunopathology and bone destruction (Moutsopoulos et al., 2015b). Experimental studies in animal models strongly support a pathogenic role for IL-17 in periodontitis. IL-17 blockade has been shown to reverse immunopathology linked to excessive neutrophil recruitment in Del-1-deficient mice (Eskan et al., 2012). Likewise, in mouse models of LADI periodontitis (LFA-$1^{KO}$) inhibition of IL-17 or IL-23p19 was able to arrest inflammatory bone loss (Moutsopoulos et al., 2014). However, human studies targeting the IL-17 cytokine pathway are necessary to conclusively define the role of IL-17 in the pathogenesis and progression of periodontal diseases.

## What is the role of IL-17surveillance in the establishment of the oral microbiome

IL-17 has emerged as a critical cellular regulator of mucosal immunity and inflammation at the oral barrier. Given the well-recognized role of the commensal microbiome in health and disease it becomes important to understand what the role of IL-17 immunity is in shaping microbiome colonization in the oral cavity. To date it is well appreciated that IL-17 responses are critical for fungal surveillance in the oral cavity, particularly for surveillance of oral *Candida*. Yet, little is known of the role of IL-17 responses in microbiome/bacterial surveillance. Interestingly, despite the fact that IL-17 signaling has been shown to participate in immunity against bacterial pathogens at various tissue sites (Isailovic et al., 2015), data from various PID patient cohorts with disruptions in Th17 immunity do not indicate susceptibility to any other oral infections in patients with blunted Th17 responses. Yet one cannot disregard a possible role for the microbiome as a contributor in the susceptibility to oral candidiasis. The interplay between microbiome and mycobiome is a well-recognized factor in the control of fungal infections as evidenced by the increase in fungal mucosal infections in patients following antibiotics (Sobel, 2007, Diaz et al., 2014). Therefore, evaluating microbiome/mycobiome interactions in the setting of defective IL-17 immunity becomes of greater interest.

Interestingly, while the oral microbiome in the setting of reduced IL-17 immunity is only recently beginning to be evaluated (Smeekens et al., 2014), it is well documented that exaggerated IL-17 oral responses are linked to microbial overgrown and dysbiosis (Figure 5). Exaggerated IL-17 production in the context of chronic and LAD-1 periodontitis is accompanied by an increase in microbial load and presence of dysbiotic bacterial communities (Eskan et al., 2012, Moutsopoulos et al., 2015a, Abusleme et al., 2013). However, strong evidence supporting a role for exaggerated IL-17 inflammation in facilitating the formation of dysbiotic microbial communities comes from animal models of LAD-1 periodontitis. Murine LAD-1 (LFA-$1^{KO}$) is associated with an increase in oral

microbial load and anaerobic counts. Importantly, inhibition of IL-17 or IL-23 alone (without restoration of the genetic defect) reverses microbial dysbiosis suggesting that exaggerated IL-17 inflammation is a driving force for microbial imbalance in periodontitis (Moutsopoulos et al., 2014). It has been theorized previously that the microbial communities associated with periodontitis have an ‘inflammophilic’ character and thrive in the presence of inflammation and its nutrients (Hajishengallis, 2014). In accordance with this hypothesis and data from experimental models, in humans it has been shown that periodontal inflammation drives an increase in microbial load in periodontitis (Abusleme et al., 2013). It is possible (based on data from the LAD model) that amplification of the IL-17 axis is a critical component of periodontal inflammation which facilitates a shift towards a “pathogenic” microbial community. However, further studies in humans targeting the IL-17 response can only conclusively define the role of IL-17 in the pathogenesis of periodontitis and its contribution to microbial dysbiosis.

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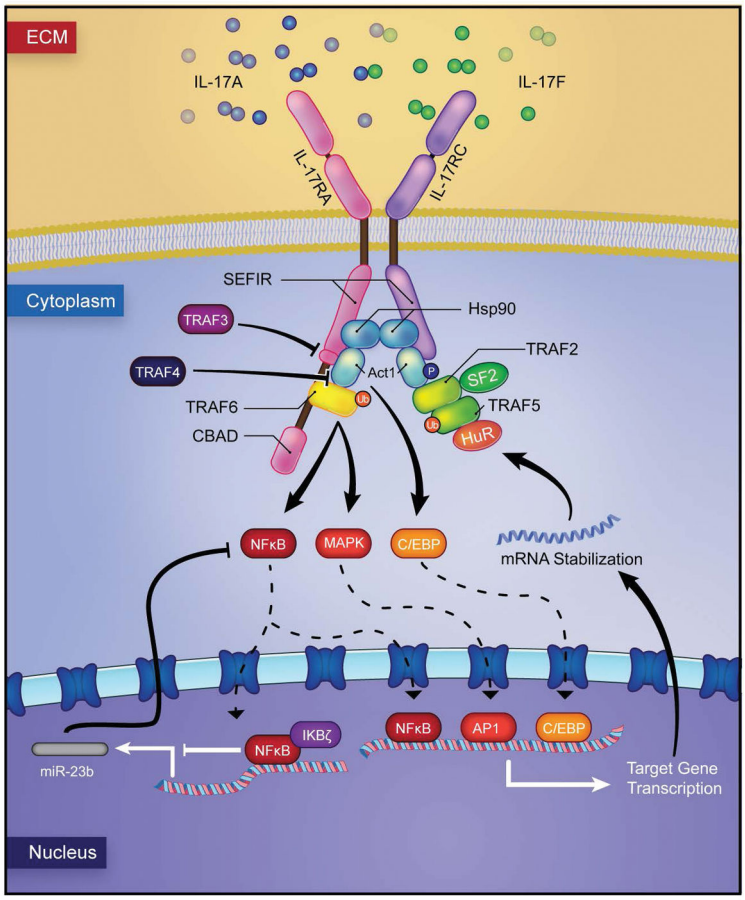


**Figure 1. The IL-17 signaling**

IL-17 (IL-17A, IL-17F, IL-17A/F) engages the heteromeric IL-17R complex and recruits the adaptor protein Act1. Act1 triggers the ubiquitination of TRAF6. TRAF6 activates three major pathways namely NF-κB, MAPK and C/EBP, triggering the transcription of IL-17 target genes. This signaling cascade is regulated at multiple steps. Hsp90 acts as a positive regulator of this cascade by stabilizing Act1. TRAF2 and TRAF5 are also positive regulators that form a complex with SF2 and recruit HuR, to mediate mRNA stabilization. TRAF3 inhibits the association of the IL-17R with Act1 and TRAF4 inhibits the recruitment of TRAF6 by Act1. miR-23b negatively regulates NF-κB activation.

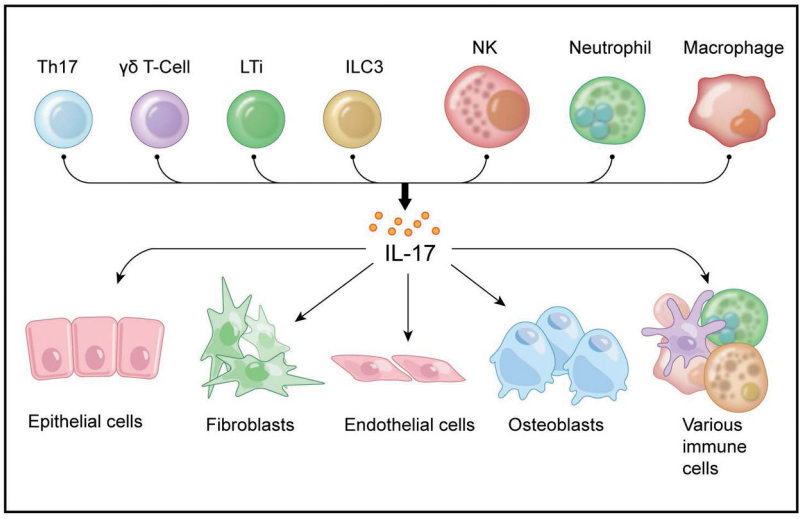


**Figure 2. Cellular sources and targets of IL-17**

(**Upper panel**) Main cellular sources of IL-17 are Th17 cells and other immune cells such as γδ T cells, lymphoid tissue inducer cells (LTi), innate lymphoid cells type 3 (ILC3s) and natural killer cells (NK). During inflammation IL-17 can also be produced by neutrophils and macrophages. (**Lower panel**) Cellular targets of IL-17 are primarily non-hematopoietic cells, including keratinocytes, fibroblasts, endothelial and osteoblasts cells. Immune cells such as T, B and NK cells can also be IL-17 targets.

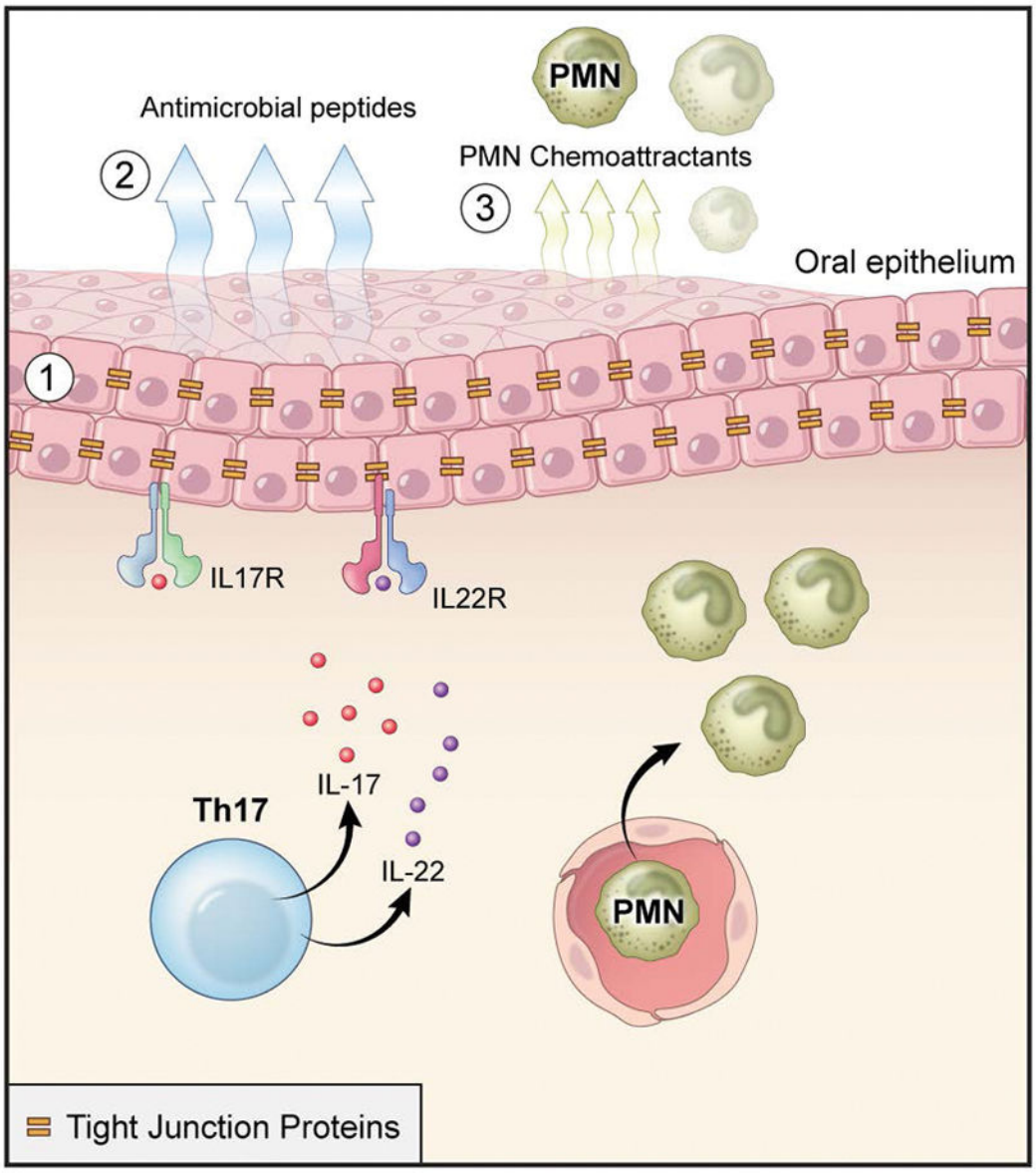


**Figure 3. IL-17 is critical for oral mucosal integrity and immunosurveillance**

Th17 cells, largely through its effector cytokine IL-17 (but also through IL-22), have an important role in maintaining mucosal barrier integrity. Key functions in IL-17-mediated mucosal surveillance are (1) regulation of epithelial tight junction protein expression (2), induction of antimicrobial peptide production (3) and release of neutrophil chemo-attractants.

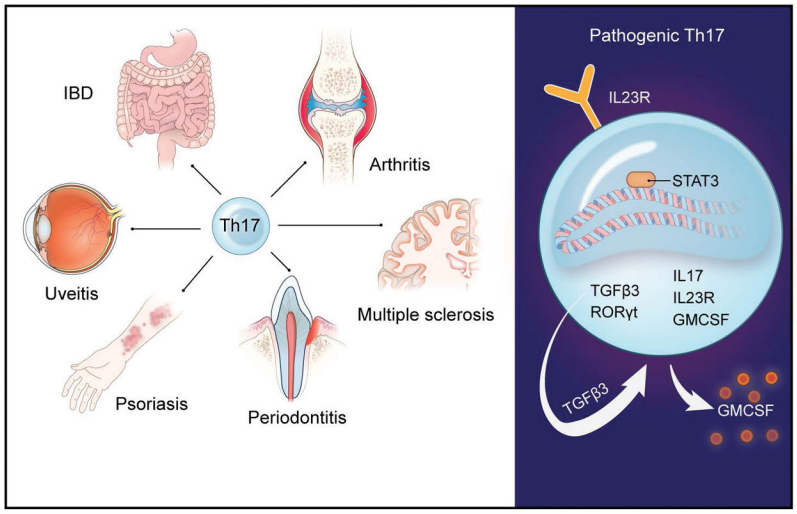


**Figure 4. Th17 in inflammatory disease and their pathogenic Th17 signature**

(**Left**) Th17 cells have been implicated in the pathogenesis of various inflammatory and autoimmune diseases. (**Right**) Cellular and molecular signature of pathogenic Th17 cells.

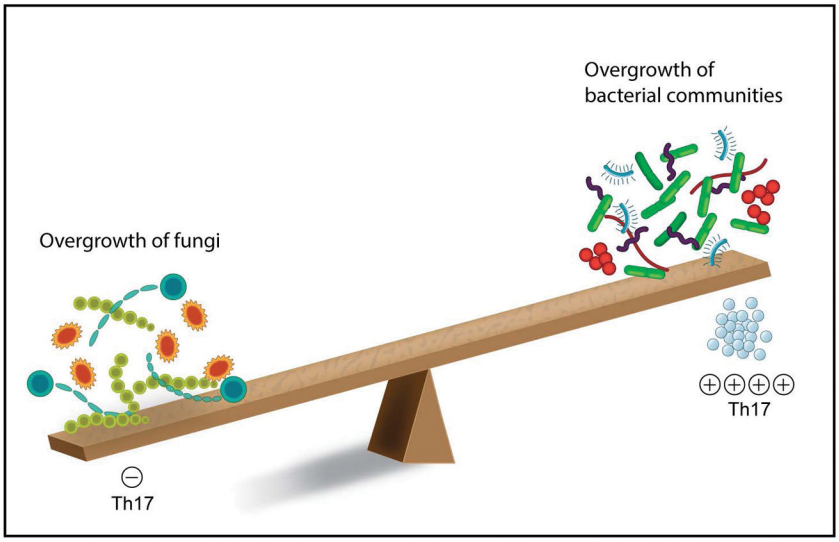


**Figure 5. Concepts of how IL-17 immunity may participate in the establishment of the oral microbiome/mycobiome**

Defects in the Th17 pathway are associated with an overgrowth of fungi leading to oral and mucocutaneous candidiasis. Conversely, exaggerated IL-17 responses in the context of periodontitis have been linked to bacterial overgrowth and dysbiosis.

## Table 1

Primary Immunodeficiencies Affecting the Th17 Cell Pathway Linked to Susceptibility to Oral Mucosal Infection.

| Oral manifestation | Gene affected by mutation | Clinical Syndrome (If described) | Reference |
|---|---|---|---|
| Chronic Mucocutaneous Candidiasis (CMC) | *IL-17RA, IL-17RC*<br>*IL-17F, ACT1* | | (Puel et al., 2011)<br>(Boisson et al., 2013)<br>(Ling et al., 2015) |
| | Loss-of -function *STAT3* | Autosomal dominant hyper IgE syndrome (AD-HIES) | (Freeman & Holland, 2009) |
| | Gain-of-function *STAT1* | | (Liu et al., 2011) |
| | *AIRE* | Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) | (Meloni et al., 2012) |
| | *DOCK8* | Autosomal recessive hyper IgE syndrome (AR-HIES) | (Zhang et al., 2009) |
| | *DECTIN-1* | | (Ferwerda et al., 2009) |
| | *CARD-9* | | (Glocker et al., 2009) |
| | *IRF8* | | (Hambleton et al., 2011) |
| | *STK4* | | (Abdollahpour et al., 2012) |
| | *CD45, IL7RA, RAG1, RAG2, ADA, AK2*<br>*JAK3, ARTEMIS* | Severe combined immunodeficiency (SCID) | (Buckley, 2004) |