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Th17 immunity in health and disease

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The contrasting roles of Th17 immunity in human health and disease¹

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List of Abbreviations:

CSF, cerebrospinal fluid; CyTOF, cytometry by time of flight; IBD, inflammatory

bowel disease; ILC, innate-like lymphoid cell; iTreg, inducible T regulatory cell;

MS, multiple sclerosis; nTreg, natural T regulatory cell; RA, rheumatoid arthritis;

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ROR, related orphan receptor; Teff, T effector cell; TGF, transforming growth factor; Treg, T regulatory cell; WCV, whole cell vaccine.

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Abbreviations

Key words: autoimmune, IL-17, infection, inflammation, pneumococcal

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ABSTRACT

The human immune system is a tightly regulated network that protects the host from disease. An important aspect of this is the balance between pro-inflammatory Th17 cells and anti-inflammatory T regulatory (Treg) cells in maintaining immune homeostasis. Foxp3⁺ Treg are critical for sustaining immune tolerance through IL-10 and transforming growth factor- β while related orphan receptor- γ ⁺ Th17 cells promote immunopathology and auto-inflammatory diseases through the actions of IL-17A, IL-21 and IL-22. Therefore, imbalance between Treg and Th17 cells can result in serious pathology in many organs and tissues. Recently, certain IL-17-producing cells have been found to be protective against infectious disease, particularly in relation to extracellular bacteria such *Streptococcus pneumoniae*; a number of other novel IL-17-secreting cell populations have also been reported to protect against a variety of other pathogens. In this mini-review, the dual roles of Treg and Th17 cells are discussed in the context of autoimmunity and infections, highlighting recent advances in the field. Development of novel strategies specifically designed to target these critical immune response pathways will become increasingly important in maintenance of human health.

Key words: autoimmune, IL-17, infection, inflammation, pneumococcal.

Introduction

In 1986, Mossman and Coffman introduced the concept of distinct CD4 T helper cell lineages based on the types of cytokines that were produced when stimulated; they, broadly classified these as Th1 and Th2 lymphocytes. Th1 cells

are characterized by the production of IFN- γ and induce cell-mediated immunity against intracellular pathogens, whereas Th2 cells produce IL-4 and stimulate humoral immunity (1). This concept was maintained until 2005, when a third T helper subset, known as Th17, was identified (2). Th17 cells, characterized by the production of IL-17, have been shown to play an essential role in the pathogenesis of several inflammatory and autoimmune diseases, including such as multiple sclerosis (MS), rheumatoid arthritis (RA), and inflammatory bowel diseases (IBDs) (3, 4).

Regulation of Th17 cells is mediated by CD4⁺ regulatory T cells (Treg) cells, which were first identified in 2001. Since their discovery, Tregs have been shown to be essential for the maintenance of tolerance; they, therefore, have a critical role in the prevention of allergy and autoimmune diseases (5, 6). Several Treg subsets have been described, including nTregs, which originate from the thymus, and iTregs, which are found in peripheral lymphoid tissues (7). CD4⁺ naive T cell precursors differentiate into various effector Th helper cells largely depending on the cytokine signals they receive in the tissue microenvironment. The failure to regulate cytokine signalling potentially results in the imbalance of various Th helper cell subsets, leading to the development of inflammatory states.

Roles of cytokines in the Th17 and Treg developmental pathways

Murine studies have shown that Treg and Th17 differentiation from naive CD4⁺ T cells is reciprocally regulated (8). Th17 cells are differentiated in the presence

of IL-6 and TGF- β whereas IL-1 β is also required in humans (2, 9). Although IL-23 was initially thought to be a key component of the Th17 differentiation pathway, recent studies have shown that this cytokine is crucial for the expansion, survival and stability of this T helper subset (10). These cytokines drive the signal transducer and activator of transcription 3 pathway, which is essential for differentiation of Th17 cells (11). Upon differentiation, these cells express a unique transcription factor, RORC in humans or ROR γ t in mice, and secrete a characteristic profile of cytokines, including IL-17A, IL-17F, IL-21, TNF- α and IL-22 (3).

The identification of two distinct populations of Th17 cells could explain these cells' dual roles. They have been categorized as pathogenic Th17 cells, termed Teff17, and beneficial or protective Th17 cells, termed Treg17 (12). Teff17 reportedly requires IL-23: studies have shown that IL-23 and IL-23R knockout mice are not susceptible to developing autoimmunity (13, 14). Teff17 differentiated cells cause type 1 diabetes when they are adoptively transferred to non-obese diabetic mice, demonstrating their pathogenic nature. In contrast, development of Treg17 requires TGF- β and has been shown to suppress pathogenic T cells in non-obese diabetic mice, inhibit granulocyte macrophage-colony stimulating factor, a pathogenic cytokine, and induce IL-10 secretion, which protects against tissue inflammation (14). Th17 skewing from Tregs is less well understood; however, Tregs have been shown to have the capacity to secrete IL-17 and express ROR γ t (15). It remains unclear which factors or

mechanisms are responsible for IL-17 secretion and ROR γ t expression in these Tregs.

Control of Th17 responses by Tregs is well recognized (16), expression of the lineage-specific transcription factor Foxp3 being the key to suppressing proliferation of effector T cells such as Th1, Th2 and Th17. There are several classes of Tregs. nTregs originate from the thymus whereas iTregs are derived from the periphery; both express Foxp3. iTregs are differentiated from CD4 naive cells in the peripheral circulation upon cellular activation in the presence of TGF- β . However, in contrast to nTregs, the iTregs phenotype is less stable in that they can both acquire and lose Foxp3 expression, this being highly dependent on the regulatory condition of the host (17). This has been further highlighted by studies under lymphopenic conditions, where IL-2 availability is limited, which have found that a larger proportion of iTregs than nTregs lose Foxp3 expression (18). Therefore, maintenance of a fine balance along the Th17/Treg axis is critical in protecting against autoimmune and inflammatory diseases.

The role of cytokines in modulating the Th17/Treg pathway has been reinforced by many studies. These studies have demonstrated that inhibition of IL-6 and TNF- α signaling increases the ratio of Tregs to Th17 cells during treatment of patients with RA (19, 20). These data suggest regulating the balance of key cytokines can tilt the ratio of Tregs to Th17 cells and that this is important in the treatment of RA. Similarly, skewing towards a Th17 phenotype during infection

could also be beneficial, suggesting that these responses must be precisely regulated to confer beneficial effects on the host (Fig. 1). Improved understanding of the various factors and conditions that favor development and regulation of the Th17 and Treg pathways will assist development of novel therapeutics for restoring the Th17/Treg axis in different pathological settings.

Pathogenic role of Th17 responses during autoimmune disease

Th17 cells are instrumental in contributing to the pathogenesis of autoimmune diseases such as MS, RA, psoriasis and IBD (16, 21-23). For example, serum and CSF from patients with MS have high concentrations of IL-17 (24-26). A recent study showed that human CD4⁺ T cells differentiated towards a Th17 phenotype have a greater capacity than Th1 differentiated cells to penetrate the blood brain barrier and infiltrate the parenchyma of the central nervous system (27). It has been shown that human blood brain barrier endothelial cells more weakly express tight junction proteins following culture with recombinant IL-17, thus allowing transmigration of CD4⁺ T cells and other inflammatory cells into the central nervous system. The role of Th17 cells in the pathogenesis of RA has also been demonstrated (28), animal studies having shown that IL-17 is present in inflamed joints and that Th17 cells are the dominant type T cell involved in pathogenesis of chronic erosive disease (29). In humans, it has been found that patients with RA have a greater frequency of Th17 cells than healthy controls, reinforcing the pathogenic nature of Th17 cells in RA (30, 31). Further evidence can be gleaned from patients with IBD, in whom both high numbers of peripheral blood Th17 cells and high IL-17A concentrations within

the intestinal mucosa have been detected (32). In contrast, these patients have small numbers of Tregs, providing further evidence for the role of the Th17/Treg axis.

Tregs play a pivotal role in the prevention of these Th17-mediated autoimmune diseases (16, 21, 33). In the context of autoimmunity, Tregs exert their suppressive function in a cell–cell contact-dependent fashion with release of IL-35 and inhibition of proliferation of pathogenic Th17 cells (21, 34, 35). For example, patients with RA undergoing anti-TNF α treatment reportedly have increased numbers of Tregs that can suppress pathogenic Th17 responses (36). Similarly, anti-TNF- α treatment of patients with IBD results in increased peripheral Treg expression (37). Other studies have also shown inhibition of Th17 responses by Tregs in terms of frequency and cytokine production (21, 38).

Protective role of Th17 responses during infection with *Streptococcus pneumoniae*

It is clear that while Th17 cells have pathogenic properties, not all actions by Th17 cells are deleterious; they have also been shown to confer protection against infections with extracellular bacteria such as *Streptococcus pneumoniae*.

The gram-positive bacterium *S. pneumoniae* (pneumococcus) causes significant morbidity and mortality in children under the age of five world-wide

(39) via a range of diseases including meningitis, bacteremia and pneumonia (40). The importance of CD4⁺ Th17 cells in protection against pneumococcal infections at the mucosa has become increasingly recognized (41). Many studies support a key role for Th17 responses in preventing or reducing pneumococcal carriage in mouse models and in humans (40, 42, 43). Th17 cells secrete the pro-inflammatory cytokine IL-17, which is essential for recruitment and activation of macrophages and neutrophils to the nasopharynx, which is in turn critical for clearance of this organism from the host (44).

Nasopharyngeal colonization, which is asymptomatic in most cases, is the first step in disease pathogenesis. Colonization induces an inflammatory response which, when unregulated, can lead to excessive mucosal damage and dissemination to other sites in the host and facilitate transmission between individuals. Th17-mediated immunity has emerged as a key factor in protection against colonization and lung pathology, whereas the presence of serotype-specific IgG is a correlate of vaccine-induced protection against invasive disease (42, 45, 46). The importance of IL-17-secreting Th17 cells has been highlighted by the finding that these cells orchestrate recruitment and activation of neutrophils, monocytes and macrophages to sites of inflammation in the upper respiratory tract, leading to the clearance of pneumococci (45). Moreover, prior colonization induces both systemic IgG and lung IL-17A responses that reduce the duration of subsequent carriage events and inhibit development of invasive pneumococcal disease (47). Although systemic and mucosal antibodies also contribute to protection, the protection against lung infection

afforded by prior colonization is lost in the absence of CD4+ T cells or IL-17 (48). Importantly, it has been found that the site(s) of subsequent infection determine the basis of protection, Th17 responses being critical against lung infection whereas antibodies are needed against invasive infection (49). However, IL-17-based protection against pneumococcal infections seems to be diminished or lost when preceded by a viral infection such as influenza (50). The reasons for this are not fully understood; however, it may involve viral upregulation of interferon signaling, which in turn negatively regulates IL-17 responses to bacterial infections (51). Therefore an important avenue of future research is how IL-17A responses can be modulated in the presence of viral infections, especially with influenza or respiratory syncytial virus.

A protective role of IL-17 in humans is supported by the following findings. IL-17 is produced following *in vitro* stimulation of tonsillar and peripheral blood mononuclear cells with pneumococcal antigens such as pneumolysin and whole cell antigen (42, 46, 52). The protective effect of IL-17 is mediated through enhanced opsonophagocytic killing of pneumococci by human neutrophils in the absence of antibodies and complement and is abrogated in the absence of IL-17A receptors. Moreover, our group and others have shown that high IL-17 concentrations are associated with low pneumococcal nasopharyngeal carriage density in mice and children (42, 53-55). It was recently found that mucosal Tregs isolated from children with pneumococcal carriage are more numerous than in children without pneumococcal carriage and exhibit potent inhibitory effects on CD4+ T cell proliferation (56). Interestingly, compared with children who are not colonized, young children (<6 years of age) colonized with

pneumococcus have significantly more Tregs with an effector/memory phenotype that inhibits pneumococcal T cell responses in their adenoids or tonsils (43, 57). Stimulation with pneumococcal whole cell antigen induces proliferation of Tregs and production of IL-10 but not IL-17. This is reversed following Treg depletion, resulting in IL-17 secretion. Furthermore, the amounts of Th17 and Treg in nasal-associated lymphoid tissue are inversely correlated, amounts of Th17 increasing with age and being greater in carriage-negative individuals (58). In contrast, mice that are resistant to pneumococcal pneumonia have significantly more numerous Tregs in their lungs than mice with invasive pneumonia, this being mediated through TGF- β signaling (56). These data suggest that maintenance of Th17/Treg balance is critically important in control of pneumococcal colonization. More studies to confirm these effects during pneumococcal infection and disease in humans are needed.

That identification of IL-17 responses is critical for protection against pneumococcal infection has led to significant efforts in developing effective vaccines to enhance these responses. Over the past decade, a pneumococcal WCV has entered Phase I and Phase II clinical trials in Indonesia and Kenya after being shown to specifically induce IL-17 immunity and prevent pneumococcal infections in mice (59). This vaccine is based on an unencapsulated strain of *S. pneumoniae* and, unlike current pneumococcal conjugate vaccines, offers the advantage of providing serotype-independent protection (60). The outcome of the currently ongoing WCV trials will not be known for some time but they will likely lead to a major shift in current pneumococcal prevention strategies.

Non-Th17 sources of IL-17 in host protection

Various cell types other than Th17, including $\gamma\delta$ T cells and ILCs, produce IL-17 (61). It has been shown that rapid induction of IL-17-producing $\gamma\delta$ T cells in the oral cavity is essential for control of candida infection (62). This has also been demonstrated in *C. albicans*-treated human DCs, specific V γ 1-responsive cells being required to produce substantial amounts of IL-17 (63). Other studies have shown that the major type of cell that migrates to the lungs of mice during sepsis and produces IL-17 to control inflammatory responses (64) and schistosomal infection is V γ 4 T cell receptor-expressing cells (65). During influenza virus infection, IL-17 production by $\gamma\delta$ T cells, but not Th17 cells, is controlled by IL-21R signaling, suggesting distinct pathways of IL-17 regulation (66). For pneumococcal infection, both IL-17 produced by $\gamma\delta$ T cells and B cells are involved in the protection mediated by an experimental gamma-irradiated whole cell vaccine (67), supporting the contention that other sources of IL-17 may be equally important in host protection from bacterial disease. However, $\gamma\delta$ -IL-17-mediated pathology can also occur, as demonstrated in a mouse model of liver inflammation (68). Thus, rigorous examination of the safety of potential new therapies aimed at augmenting these responses is necessary.

Interestingly, ILCs also mediate protection against fungal infection through IL-17 production in mice in an IL-23 dependent manner (69). A distinct subset of ILCs that produce IL-17 in the mucosa, ILC17, become less numerous during simian immunodeficiency virus infection of macaques, implying they play a role in host protection (70). A recent study also showed that B cells are primary producers

of IL-17 during infection with the protozoan parasite, *Trypanosoma cruzi*, and are able to confer protection (71). This was shown to be mediated by exposure of B cells to the trans-sialidase enzyme secreted by the parasite, upon which they secrete IL-17. Similarly, isolated human B cells stimulated with this enzyme significantly increase their IL-17 production. Whether such effects of B cells occur in other infections, particularly with *S. pneumoniae*, which also express trans-sialidase (72), is intriguing. Patients with RA more frequently have IL-17-secreting B cells than healthy controls, as well as other non-T cell sources such as NK and CD14+ cells, suggesting a heterogeneous cellular source of IL-17 (28).

There is also some evidence that Foxp3+ T cells are converted to pathogenic Th17 cells via IL-6 in the context of autoimmune arthritis (73, 74), contributing to its pathogenesis. Other studies have shown that this can also occur in the presence of enhanced TNF- α signaling (19, 75). New insights into the role of mucosal-associated invariant T cells have also shed light on their role during infection. Increased MHC-related 1+ mucosal associated invariant T cells accumulate in the lung of mice following *S. typhimurium* infection and can be stimulated by co-stimulatory signals to promote clearance (76). However, further research to elucidate the differing roles of these novel subsets during infection and immune pathology is needed (77).

Systems biology to enhance understanding of protective immunity

As we begin to unravel the complex mechanisms that underpin disease pathogenesis, the need for high-throughput sophisticated technologies has never been more paramount. Manipulation of Th17 responses to promote health will require substantial efforts toward developing more effective and targeted therapies. This is especially true for development of novel vaccines and therapeutics that require rigorous preclinical and human trials. Systems biology has been used successfully to identify host transcriptome signatures associated with protective immune responses following vaccination (78, 79). This approach, which involves both metabolic and/or cell signaling networks and mathematical and computational models, can enhance our understanding of biological pathways associated with vaccination and protective host responses (80). Recently, CyTOF, a variation of flow cytometry in which antibodies are labelled with heavy metal ion tags rather than fluorochromes, has yielded significant results regarding host responses. This technique allows quantification of protein (chemokine and cytokine) expression on a single cell level (81). Advantages of this platform offers include tracking kinetics of cellular trafficking and studying interactions between many phenotypically and diverse immune cell subsets (82). For example, a recent study using CyTOF found that identification of a unique $\gamma\delta$ T cell subset expressing Ly-6G myeloid differentiation antigen enabled distinguishing between IL-17A- and IFN- γ -producing cells in the lungs of *S. pneumoniae* infected mice (83).

These novel approaches are exciting means of advancing understanding of how Th17 responses can be enhanced in the context of infection or controlled during

autoimmunity. Moreover, in the context of pneumococcal infection, it would be very useful to use this strategy to examine responses to WCV (84, 85), dissect IL-17-inducing capacity among various cell types, and determine how these responses differ across immunological compartments within a host (e.g., blood vs. mucosal surfaces). Importantly, these approaches can identify individuals who will have poor treatment outcomes or be non-responsive to vaccines. In this context, strategies that effectively modulate Th17 immunity will be critically important for accelerating vaccine and drug development programs.

CONCLUSIONS

Our understanding of the role of Th17 responses in both pathogenic and protective immunity has increased substantially over the last decade. Importantly, the signals needed to promote or control IL-17 secretion and identification of non-Th17 sources of IL-17 will enable new-generation therapies to be developed for a range of autoimmune and inflammatory conditions as well as for infection. Advances in 'omics' technologies have allowed researchers to investigate intricate pathways and immune networks in ways that were hitherto impossible. Future studies using these sophisticated technologies to focus on human responses to novel Th17 vaccines and other Th17-modifying drugs are essential and will achieve a more complete understanding of the role of Th17 (and Tregs) in health and disease.

DISCLOSURE

No authors declare a conflict of interest.

References

1 Kaiko G.E., Horvat J.C., Beagley K.W., Hansbro P.M. (2008) Immunological decision-making: how does the immune system decide to mount a helper T-cell response? *Immunology* **123**: 326-38.

2 Marwaha A.K., Leung N.J., McMurchy A.N., Levings M.K. (2012) TH17 cells in autoimmunity and immunodeficiency: Protective or pathogenic? *Front Immunol* **3**: 129.

3 Waite J.C., Skokos D. (2012) Th17 response and inflammatory autoimmune diseases. *Int J Inflamm* **2012**: 819467.

4 Noack M., Miossec P. (2014) Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. *Autoimmun Rev* **13**: 668-77.

5 Buckner J.H. (2010) Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases. *Nat Rev Immunol* **10**: 849-59.

6 Carrier Y., Yuan J., Kuchroo V.K., Weiner H.L. (2007) Th3 cells in peripheral tolerance. II. TGF-beta-transgenic Th3 cells rescue IL-2-deficient mice from autoimmunity. *J Immunol* **178**: 172-8.

7 Campbell D.J., Koch M.A. (2011) Phenotypical and functional specialization of FOXP3+ regulatory T cells. *Nat Rev Immunol* **11**: 119-30.

8 Horwitz D.A., Zheng S.G., Gray J.D. (2008) Natural and TGF-beta-induced Foxp3(+)CD4(+) CD25(+) regulatory T cells are not mirror images of each other. *Trends Immunol* **29**: 429-35.

9 Korn T., Bettelli E., Oukka M., Kuchroo V.K. (2009) IL-17 and Th17 Cells. *Annu Rev Immunol* **27**: 485-517.

10 Peck A., Mellins E.D. (2010) Plasticity of T-cell phenotype and function: the T helper type 17 example. *Immunology* **129**: 147-53.

11 Zheng S.G. (2013) Regulatory T cells vs Th17: differentiation of Th17 versus Treg, are they mutually exclusive? *Am J Clin Exp Immunol* **2**: 94-106.

12 Battaglia M., Gregori S., Bacchetta R., Roncarolo M.G. (2006) Tr1 cells: From discovery to their clinical application. *Semin Immunol* **18**: 120-7.

13 Astier A.L., Meiffren G., Freeman S., Hafler D.A. (2006) Alterations in CD46-mediated Tr1 regulatory T cells in patients with multiple sclerosis. *J Clin Invest* **116**: 3252-7.

14 Cottrez F., Hurst S.D., Coffman R.L., Groux H. (2000) T regulatory cells 1 inhibit a Th2-specific response *in vivo*. *J Immunol* **165**: 4848-53.

15 Groux H., O'Garra A., Bigler M., Rouleau M., Antonenko S., de Vries J.E., Roncarolo M.G. (1997) A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* **389**: 737-42.

16 Crome S.Q., Clive B., Wang A.Y., Kang C.Y., Chow V., Yu J., Lai A., Ghahary A., Broady R., Levings M.K. (2010) Inflammatory effects of *ex vivo* human Th17 cells are suppressed by regulatory T cells. *J Immunol* **185**: 3199-208.

17 Eisenstein E.M., Williams C.B. (2009) The T(reg)/Th17 cell balance: A new paradigm for autoimmunity. *Pediatr Res* **65**: 26R-31R.

18 Yadav M., Stephan S., Bluestone J.A. (2013) Peripherally induced tregs—role in immune homeostasis and autoimmunity. *Front Immunol* **4**: 232.

19 Nie H., Zheng Y., Li R., Guo T.B., He D., Fang L., Liu X., Xiao L., Chen X., Wan B., Chin Y.E., Zhang J.Z. (2013) Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-alpha in rheumatoid arthritis. *Nat Med* **19**: 322-8.

20 Samson M., Audia S., Janikashvili N., Ciudad M., Trad M., Fraszczak J., Ornetti P., Maillefert J.F., Miossec P., Bonnotte B. (2012) Brief report: inhibition of interleukin-6 function corrects Th17/Treg cell imbalance in patients with rheumatoid arthritis. *Arthritis Rheum* **64**: 2499-503.

21 Mondal S., Martinson J.A., Ghosh S., Watson R., Pahan K. (2012) Protection of Tregs, suppression of Th1 and Th17 cells, and amelioration of experimental allergic encephalomyelitis by a physically-modified saline. *PLoS ONE* **7**: e51869.

22 Louten J., Boniface K., de Waal Malefyt R. (2009) Development and function of TH17 cells in health and disease. *J Allergy Clin Immunol* **123**: 1004-11.

23 Patel D.D., Kuchroo V.K. (2015) Th17 cell pathway in human immunity: Lessons from genetics and therapeutic interventions. *Immunity* **43**: 1040-51.

24 Tzartos J.S., Friese M.A., Craner M.J., Palace J., Newcombe J., Esiri M.M., Fugger L. (2008) Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol* **172**: 146-55.

25 Miossec P., Korn T., Kuchroo V.K. (2009) Interleukin-17 and type 17 helper T cells. *N Engl J Med* **361**: 888-98.

26 Montes M., Zhang X., Berthelot L., Laplaud D.A., Brouard S., Jin J., Rogan S., Armao D., Jewells V., Soullillou J.P., Markovic-Plese S. (2009) Oligoclonal myelin-reactive T-cell infiltrates derived from multiple sclerosis lesions are enriched in Th17 cells. *Clin Immunol* **130**: 133-44.

27 Jadidi-Niaragh F., Mirshafiey A. (2011) Th17 cell, the new player of neuroinflammatory process in multiple sclerosis. *Scand J Immunol* **74**: 1-13.

28 Schlegel P.M., Steiert I., Kotter I., Muller C.A. (2013) B cells contribute to heterogeneity of IL-17 producing cells in rheumatoid arthritis and healthy controls. *PLoS ONE* **8**: e82580.

29 Lubberts E., Koenders M.I., van den Berg W.B. (2005) The role of T-cell interleukin-17 in conducting destructive arthritis: Lessons from animal models. *Arthritis Res Ther* **7**: 29-37.

30 Colin E.M., Asmawidjaja P.S., van Hamburg J.P., Mus A.M., van Driel M., Hazes J.M., van Leeuwen J.P., Lubberts E. (2010) 1,25-dihydroxyvitamin D3 modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis. *Arthritis Rheum* **62**: 132-42.

31 Shen H., Goodall J.C., Hill Gaston J.S. (2009) Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. *Arthritis Rheum* **60**: 1647-56.

32 Eastaff-Leung N., Mabarrack N., Barbour A., Cummins A., Barry S. (2010) Foxp3+ regulatory T cells, Th17 effector cells, and cytokine environment in inflammatory bowel disease. *J Clin Immunol* **30**: 80-9.

33 Gol-Ara M., Jadidi-Niaragh F., Sadria R., Azizi G., Mirshafiey A. (2012) The role of different subsets of regulatory T cells in immunopathogenesis of rheumatoid arthritis. *Arthritis* **2012**: 805875.

34 Josefowicz S.Z., Lu L.F., Rudensky A.Y. (2012) Regulatory T cells: mechanisms of differentiation and function. *Annu Rev Immunol* **30**: 531-64.

35 Niedbala W., Wei X.Q., Cai B., Hueber A.J., Leung B.P., McInnes I.B., Liew F.Y. (2007) IL-35 is a novel cytokine with therapeutic effects against collagen-induced arthritis through the expansion of regulatory T cells and suppression of Th17 cells. *Eur J Immunol* **37**: 3021-9.

36 McGovern J.L., Nguyen D.X., Notley C.A., Mauri C., Isenberg D.A., Ehrenstein M.R. (2012) Th17 cells are restrained by Treg cells via the inhibition of interleukin-6 in patients with rheumatoid arthritis responding to anti-tumor necrosis factor antibody therapy. *Arthritis Rheum* **64**: 3129-38.

37 Boschetti G., Nancey S., Sardi F., Roblin X., Flourie B., Kaiserlian D. (2011) Therapy with anti-TNFalpha antibody enhances number and function of

Foxp3(+) regulatory T cells in inflammatory bowel diseases. *Inflamm Bowel Dis* **17**: 160-70.

38 Fletcher J.M., Lalor S.J., Sweeney C.M., Tubridy N., Mills K.H. (2010) T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clin Exp Immunol* **162**: 1-11.

39 Moffitt K.L., Gierahn T.M., Lu Y.J., Gouveia P., Alderson M., Flechtner J.B., Higgins D.E., Malley R. (2011) T(H)17-based vaccine design for prevention of *Streptococcus pneumoniae* colonization. *Cell Host Microbe* **9**: 158-65.

40 Lundgren A., Bhuiyan T.R., Novak D., Kaim J., Reske A., Lu Y.J., Qadri F., Malley R. (2012) Characterization of Th17 responses to *Streptococcus pneumoniae* in humans: Comparisons between adults and children in a developed and a developing country. *Vaccine* **30**: 3897-907.

41 Malley R., Trzcinski K., Srivastava A., Thompson C.M., Anderson P.W., Lipsitch M. (2005) CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. *Proc Natl Acad Sci USA* **102**: 4848-53.

42 Lu Y.J., Gross J., Bogaert D., Finn A., Bagrade L., Zhang Q., Kolls J.K., Srivastava A., Lundgren A., Forte S., Thompson C.M., Harney K.F., Anderson P.W., Lipsitch M., Malley R. (2008) Interleukin-17A mediates acquired immunity to pneumococcal colonization. *PLoS Pathog* **4**: e1000159.

- 43 Zhang Q., Leong S.C., McNamara P.S., Mubarak A., Malley R., Finn A. (2011) Characterisation of regulatory T cells in nasal associated lymphoid tissue in children: Relationships with pneumococcal colonization. *PLoS Pathog* **7**: e1002175.
- 44 Marques J.M., Rial A., Munoz N., Pelay F.X., van Maele L., Leger H., Camou T., Sirard J.C., Benecke A., Chabalgoity J.A. (2012) Protection against *Streptococcus pneumoniae* serotype 1 acute infection shows a signature of Th17- and IFN-gamma-mediated immunity. *Immunobiology* **217**: 420-9.
- 45 Zhang Z., Clarke T.B., Weiser J.N. (2009) Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. *J Clin Invest* **119**: 1899-909.
- 46 Mureithi M.W., Finn A., Ota M.O., Zhang Q., Davenport V., Mitchell T.J., Williams N.A., Adegbola R.A., Heyderman R.S. (2009) T cell memory response to pneumococcal protein antigens in an area of high pneumococcal carriage and disease. *J Infect Dis* **200**: 783-93.
- 47 Richards L., Ferreira D.M., Miyaji E.N., Andrew P.W., Kadioglu A. (2010) The immunising effect of pneumococcal nasopharyngeal colonisation; protection against future colonisation and fatal invasive disease. *Immunobiology* **215**: 251-63.

48 Wilson R., Cohen J.M., Jose R.J., de Vogel C., Baxendale H., Brown J.S. (2015) Protection against *Streptococcus pneumoniae* lung infection after nasopharyngeal colonization requires both humoral and cellular immune responses. *Mucosal Immunol* **8**: 627-39.

49 Cohen J.M., Khandavilli S., Camberlein E., Hyams C., Baxendale H.E., Brown J.S. (2011) Protective contributions against invasive *Streptococcus pneumoniae* pneumonia of antibody and Th17-cell responses to nasopharyngeal colonisation. *PLoS ONE* **6**: e25558.

50 Robinson K.M., Kolls J.K., Alcorn J.F. (2015) The immunology of influenza virus-associated bacterial pneumonia. *Curr Opin Immunol* **34**: 59-67.

51 Shahangian A., Chow E.K., Tian X., Kang J.R., Ghaffari A., Liu S.Y., Belperio J.A., Cheng G., Deng J.C. (2009) Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. *J Clin Invest* **119**: 1910-20.

52 Schmid P., Selak S., Keller M., Luhan B., Magyarics Z., Seidel S., Schlick P., Reinisch C., Lingnau K., Nagy E., Grubeck-Loebenstein B. (2011) Th17/Th1 biased immunity to the pneumococcal proteins PcsB, StkP and PsaA in adults of different age. *Vaccine* **29**: 3982-9.

53 Malley R., Trzcinski K., Srivastava A., Thompson C.M., Anderson P.W., Lipsitch M. (2005) CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. *Proc Natl Acad Sci USA* **102**: 4848-53.

54 Zhang Q., Arnaoutakis K., Murdoch C., Lakshman R., Race G., Burkinshaw R., Finn A. (2004) Mucosal immune responses to capsular pneumococcal polysaccharides in immunized preschool children and controls with similar nasal pneumococcal colonization rates. *Pediatr Infect Dis J* **23**: 307-13.

55 Hoe E., Boelsen L.K., Toh Z.Q., Sun G.W., Koo G.C., Balloch A., Marimla R., Dunne E.M., Tikoduadua L., Russell F.M., Satzke C., Mulholland E.K., Licciardi P.V. (2015) Reduced IL-17A secretion is associated with high levels of pneumococcal nasopharyngeal carriage in Fijian children. *PLoS ONE* **10**: e0129199.

56 Neill D.R., Fernandes V.E., Wisby L., Haynes A.R., Ferreira D.M., Laher A., Strickland N., Gordon S.B., Denny P., Kadioglu A., Andrew P.W. (2012) T regulatory cells control susceptibility to invasive pneumococcal pneumonia in mice. *PLoS Pathog* **8**: e1002660.

57 Pido-Lopez J., Kwok W.W., Mitchell T.J., Heyderman R.S., Williams N.A. (2011) Acquisition of pneumococci specific effector and regulatory Cd4+ T cells localising within human upper respiratory-tract mucosal lymphoid tissue. *PLoS Pathog* **7**: e1002396.

58 Mubarak A., Ahmed M.S., Upile N., Vaughan C., Xie C., Sharma R., Acar P., McCormick M.S., Paton J.C., Mitchell T., Cunliffe N., Zhang Q. (2016) A dynamic relationship between mucosal T helper type 17 and regulatory T-cell populations in nasopharynx evolves with age and associates with the clearance of pneumococcal carriage in humans. *Clin Microbiol Infect* **22**: 736e1-7.

59 Moffitt K.L., Malley R., Lu Y.J. (2012) Identification of protective pneumococcal T(H)17 antigens from the soluble fraction of a killed whole cell vaccine. *PLoS ONE* **7**: e43445.

60 Alderson M.R. (2016) Status of research and development of pediatric vaccines for *Streptococcus pneumoniae*. *Vaccine* **34**: 2959-61.

61 Sutton C.E., Mielke L.A., Mills K.H. (2012) IL-17-producing gammadelta T cells and innate lymphoid cells. *Eur J Immunol* **42**: 2221-31.

62 Conti H.R., Peterson A.C., Brane L., Huppler A.R., Hernandez-Santos N., Whibley N., Garg A.V., Simpson-Abelson M.R., Gibson G.A., Mamo A.J., Osborne L.C., Bishu S., Ghilardi N., Siebenlist U., Watkins S.C., Artis D., McGeachy M.J., Gaffen S.L. (2014) Oral-resident natural Th17 cells and gammadelta T cells control opportunistic *Candida albicans* infections. *J Exp Med* **211**: 2075-84.

63 Maher C.O., Dunne K., Comerford R., O'Dea S., Loy A., Woo J., Rogers T.R., Mulcahy F., Dunne P.J., Doherty D.G. (2015) *Candida albicans* stimulates IL-23 release by human dendritic cells and downstream IL-17 secretion by Vdelta1 T cells. *J Immunol* **194**: 5953-60.

64 Costa M.F., de Negreiros C.B., Bornstein V.U., Valente R.H., Mengel J., Henriques M., Benjamim C.F., Penido C. (2015) Murine IL-17+ Vgamma4 T lymphocytes accumulate in the lungs and play a protective role during severe sepsis. *BMC Immunol* **16**: 36.

65 Chen D., Luo X., Xie H., Gao Z., Fang H., Huang J. (2013) Characteristics of IL-17 induction by *Schistosoma japonicum* infection in C57BL/6 mouse liver. *Immunology* **139**: 523-32.

66 Moser E.K., Sun J., Kim T.S., Braciale T.J. (2015) IL-21R signaling suppresses IL-17+ gamma delta T cell responses and production of IL-17 related cytokines in the lung at steady state and after Influenza A virus infection. *PLoS ONE* **10**: e0120169.

67 Babb R., Chen A., Hirst T.R., Kara E.E., McColl S.R., Ogunniyi A.D., Paton J.C., Alsharifi M. (2016) Intranasal vaccination with gamma-irradiated *Streptococcus pneumoniae* whole-cell vaccine provides serotype-independent protection mediated by B-cells and innate IL-17 responses. *Clin Sci (Lond)* **130**: 697-710.

68 Klemann C., Schroder A., Dreier A., Mohn N., Dippel S., Winterberg T., Wilde A., Yu Y., Thorenz A., Gueler F., Jorns A., Tolosa E., Leonhardt J., Haas J.D., Prinz I., Vieten G., Petersen C., Kuebler J.F. (2016) Interleukin 17, produced by gammadelta t cells, contributes to hepatic inflammation in a mouse model of biliary atresia and is increased in livers of patients. *Gastroenterology* **150**: 229-41e5.

69 Gladiator A., Wangler N., Trautwein-Weidner K., LeibundGut-Landmann S. (2013) Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection. *J Immunol* **190**: 521-5.

70 Xu H., Wang X., Liu D.X., Moroney-Rasmussen T., Lackner A.A., Veazey R.S. (2012) IL-17-producing innate lymphoid cells are restricted to mucosal tissues and are depleted in SIV-infected macaques. *Mucosal Immunol* **5**: 658-69.

71 Bermejo D.A., Jackson S.W., Gorosito-Serran M., Acosta-Rodriguez E.V., Amezcua-Vesely M.C., Sather B.D., Singh A.K., Khim S., Mucci J., Liggitt D., Campetella O., Oukka M., Gruppi A., Rawlings D.J. (2013) *Trypanosoma cruzi* trans-sialidase initiates a program independent of the transcription factors RORgammat and Ahr that leads to IL-17 production by activated B cells. *Nat Immunol* **14**: 514-22.

72 Kadioglu A., Weiser J.N., Paton J.C., Andrew P.W. (2008) The role of *Streptococcus pneumoniae* virulence factors in host respiratory colonization and disease. *Nat Rev Microbiol* **6**: 288-301.

73 Komatsu N., Okamoto K., Sawa S., Nakashima T., Oh-hora M., Kodama T., Tanaka S., Bluestone J.A., Takayanagi H. (2014) Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. *Nat Med* **20**: 62-8.

74 Joller N., Kuchroo V.K. (2014) Good guys gone bad: ExTreg cells promote autoimmune arthritis. *Nat Med* **20**: 15-7.

75 Nadkarni S., Mauri C., Ehrenstein M.R. (2007) Anti-TNF-alpha therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-beta. *J Exp Med* **204**: 33-9.

76 Chen Z., Wang H., D'Souza C., Sun S., Kostenko L., Eckle S.B., Meehan B.S., Jackson D.C., Strugnell R.A., Cao H., Wang N., Fairlie D.P., Liu L., Godfrey D.I., Rossjohn J., McCluskey J., Corbett A.J. (2017) Mucosal-associated invariant T-cell activation and accumulation after *in vivo* infection depends on microbial riboflavin synthesis and co-stimulatory signals. *Mucosal Immunol* **10**: 58-68.

77 Treiner E., Liblau R.S. (2015) Mucosal-associated invariant T cells in multiple sclerosis: the jury is still out. *Front Immunol* **6**: 503.

78 Li S., Roupael N., Duraisingham S., Romero-Steiner S., Presnell S., Davis C., Schmidt D.S., Johnson S.E., Milton A., Rajam G., Kasturi S., Carlone G.M., Quinn C., Chaussabel D., Palucka A.K., Mulligan M.J., Ahmed R., Stephens D.S., Nakaya H.I., Pulendran B. (2014) Molecular signatures of antibody responses derived from a systems biology study of five human vaccines. *Nat Immunol* **15**: 195-204.

79 Querec T.D., Akondy R.S., Lee E.K., Cao W., Nakaya H.I., Teuwen D., Pirani A., Gernert K., Deng J., Marzolf B., Kennedy K., Wu H., Bennouna S., Oluoch H., Miller J., Vencio R.Z., Mulligan M., Aderem A., Ahmed R., Pulendran B. (2009) Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. *Nat Immunol* **10**: 116-25.

80 Obermoser G., Presnell S., Domico K., Xu H., Wang Y., Anguiano E., Thompson-Snipes L., Ranganathan R., Zeitner B., Bjork A., Anderson D., Speake C., Ruchaud E., Skinner J., Alsina L., Sharma M., Dutartre H., Cepika A., Israelsson E., Nguyen P., Nguyen Q.A., Harrod A.C., Zurawski S.M., Pascual V., Ueno H., Nepom G.T., Quinn C., Blankenship D., Palucka K., Banchereau J., Chaussabel D. (2013) Systems scale interactive exploration reveals quantitative and qualitative differences in response to influenza and pneumococcal vaccines. *Immunity* **38**: 831-44.

81 Bendall S.C., Simonds E.F., Qiu P., Amir el A.D., Krutzik P.O., Finck R., Bruggner R.V., Melamed R., Trejo A., Ornatsky O.I., Balderas R.S., Plevritis

S.K., Sachs K., Pe'er D., Tanner S.D., Nolan G.P. (2011) Single-cell mass cytometry of differential immune and drug responses across a human hematopoietic continuum. *Science* **332**: 687-96.

82 Newell E.W., Sigal N., Bendall S.C., Nolan G.P., Davis M.M. (2012) Cytometry by time-of-flight shows combinatorial cytokine expression and virus-specific cell niches within a continuum of CD8+ T cell phenotypes. *Immunity* **36**: 142-52.

83 Wanke-Jellinek L., Keegan J.W., Dolan J.W., Lederer J.A. (2016) Characterization of lung infection-induced TCRgammadelta T cell phenotypes by CyTOF mass cytometry. *J Leukoc Biol* **99**: 483-93.

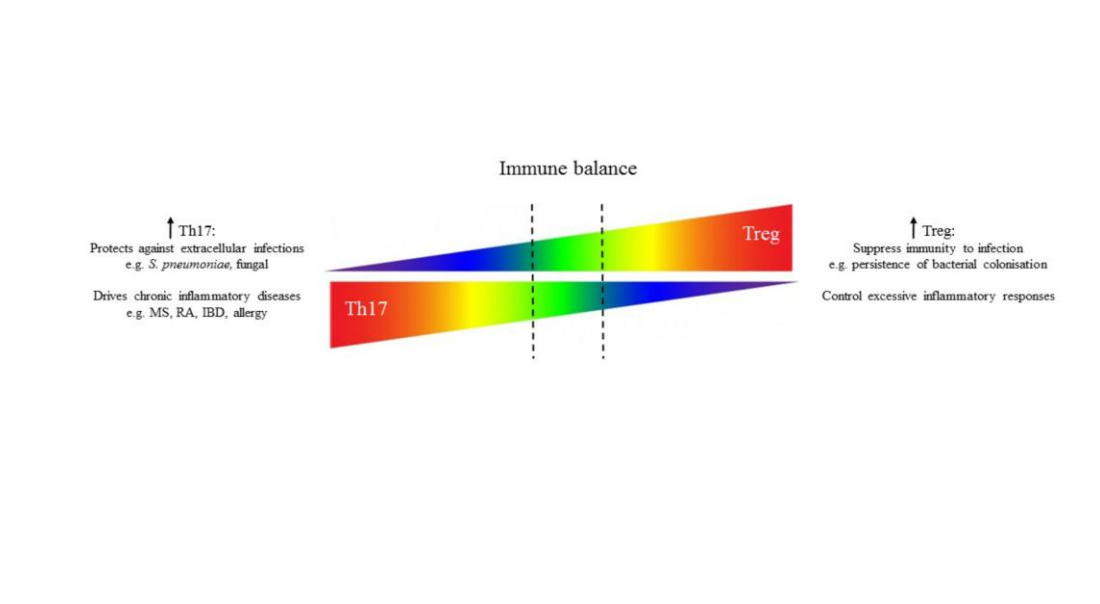
84 Goncalves V.M., Dias W.O., Campos I.B., Liberman C., Sbrogio-Almeida M.E., Silva E.P., Cardoso C.P., Jr., Alderson M., Robertson G., Maisonneuve J.F., Tate A., Anderson P., Malley R., Fratelli F., Leite L.C. (2014) Development of a whole cell pneumococcal vaccine: BPL inactivation, cGMP production, and stability. *Vaccine* **32**: 1113-20.

85 Moffitt K.L., Yadav P., Weinberger D.M., Anderson P.W., Malley R. (2012) Broad antibody and T cell reactivity induced by a pneumococcal whole-cell vaccine. *Vaccine* **30**: 4316-22.

FIGURE LEGEND

Figure 1. The relationship between Th17 and Treg cells in maintenance of health. Both these subsets have opposing effector functions in the context of autoimmune and inflammatory conditions and infection.

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