Propionibacterium acnes Strains Differentially Regulate the Fate of Th17 Responses in the Skin

Contassot, Emmanuel ; French, Lars E

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Propionibacterium acnes strains differentially regulate the fate of Th17 responses in the skin.

Emmanuel Contassot and Lars E. French

Dermatology Department, University Hospital of Zürich, Zürich, Switzerland

Correspondence:

Emmanuel Contassot, Dermatology Department, University Hospital of Zürich, Zürich, Switzerland. Email: emmanuel.contassot@usz.ch; Lars E. French, Dermatology Department, University Hospital of Zürich, Zürich, Switzerland. Email: lars.french@usz.ch

Abstract

Agak *et al*. demonstrate that different strains of *Propionibacterium acnes*, a bacterium colonizing the pilo-sebaceous unit in healthy skin and acne, have the ability to induce Th17 cells secreting either IFNγ or IL-10 and exhibiting either pathogenic or protective properties, respectively. This work contributes to the growing evidence that the phenotype of Th17 cells is largely dependent on their microbiological environment.

Bullet points

- Different *Propionibacterium acnes* strains induce pathogenic or protective Th17 responses.
- IFNγ-producing Th17 are pathogenic whereas IL-10-producting Th17 are protective.
- The use of IL-17 inhibitors may impact both pathogenic and protective Th17.

Acne is an inflammatory disorder of the pilosebaceous unit commonly occurring at puberty and affecting up to 85% of adolescents and young adults. Currently, acne is considered as a multifactorial disease involving factors such as excess sebum production, disturbed keratinization in the hair follicle, colonization of the pilosebaceous unit by the bacterium *Propionibactarium acnes* (*P. acnes*) and the release of pro-inflammatory molecules. However, although being a highly prevalent and extensively studied inflammatory skin disorder, the precise physiopathology of acne is still not completely understood.

P. acnes is an anaerobic Gram-positive bacterium present in the human skin microbiota. This commensal accumulates preferentially in pilosebaceaous units in both acne patients and healthy individuals. *P. acnes* overgrowth in acne microcomedones is associated with inflammation of the pilosebaceous unit. However, the role of this bacterium in the pathogenesis of acne has long been debated and how it contributes to acne while being a major component of the normal skin flora remains unclear. Several reports demonstrated that *P. acnes* is able to induce strong inflammatory responses by inducing the release of pro-inflammatory cytokines and chemokines in cells present in or in close proximity of the pilosebaceous unit. Keratinocytes respond to *P. acnes* exposure by releasing IL-6 and IL-8 (CXCL8), IL-1α, TNF and GM-CSF (Graham et al., 2004), while *P. acnes* stimulates the secretion of IL-1β, TNF, IL-8 and IL-12 by myeloid cells (Kistowska et al., 2013, Qin et al., 2014). Moreover, sebocytes are also responsive to *P. acnes* exposure by releasing IL-8 (CXCL8), TNF (Nagy et al., 2006) and IL-1β (Li et al., 2014).

Despite the ability of *P. acnes* to induce robust innate immune responses, cells infiltrating early acne lesions consist mainly of $CD4^+$ T cells. IL-17A-secreting $CD4^+$ T cells (Th17 cells) bridge innate and adaptive immunity and their important role in mediating host defense and controlling different microorganisms is well documented. Increasing evidence suggests that *P. acnes* is able to induce Th17 cells which may therefore contribute to

inflammation in acne. Our group and the group lead by Jenny Kim at UCLA provided experimental evidence in the past showing that the secretion of IL-17A by naïve $CD4^+$ T cells can be induced by *P. acnes* (Agak et al., 2013, Kistowska et al., 2015). We could furthermore show that IL-$17A^+$/IFN-$^{3+}$ Th17 cells - initially called "Th1/Th17" cells and also referred to as "Th1-like" cells - could be inhibited by the use of a blocking antibody to IL-1β (Kistowska et al., 2015), a cytokine that has emerged as a crucial factor driving Th17 polarization. More recently, *P. acnes*-stimulated sebocytes have been shown to promote the differentiation of naïve T cells into Th17 in a mechanism involving TGFβ, IL-6 and IL-1β (Mattii et al., 2017). In this issue, Agak *et al*. go one step further by showing that the nature and possibly the pathogenicity of *P. acnes* strains directly influence the cytokine profile of Th17 cells as well as their microbicidal properties (Agak et al., 2017). While *P. acn*es found in acne lesions induced IFNγ-secreting Th17 cells with no microbicidal activity, *P. acnes* found on healthy skin induced IL-10-secreting Th17 cells that were able to lyse *P. acnes in vitro*. In 2014, we could already show that *P. acnes* could induce both IL-$17A^+$/IFNγ^- and IL-17^+/IFNγ^+ T cells (Kistowska et al., 2015). However, since we only analyzed one strain of *P. acnes* in our study, the interesting discovery of Agak *et al*. revealing the ability of selected *P. acnes* strains to induce different Th17 cells with different cytokine secretion profiles and antimicrobial properties was missed. *P. acnes* can be classified into distinct phylotypes which are associated with healthy skin or acne. It is known since the 1980s that type I *P. acnes* is strongly associated with acne and it has been recently shown that strains of phylotypes IA-2, IB-1 and IC are also associated with acne, whereas phylotypes IB-3, II and III are associated with other tissue infections. Importantly, a very strong association has been reported between the phylotype II, ribotype 6 (II-RT6) subgroup and healthy skin, and furthermore phylotype III *P. acnes* isolates have been reported to be absent in acne lesions, but to compose approximately 20% of healthy skin isolates (Fitz-Gibbon et al., 2013, McDowell et al., 2013). The reason(s)

why RT6 *P. acnes* is exclusively present in healthy skin remain(s), however, to be determined. Constitutive differences in microbiome composition between individuals due to factors including hormone level, sebum production and changes in the pilosebaceous unit, may also account for *P. acnes* strain composition and therefore likely drive its pathogenicity. However, whether the RT6 *P. acnes* phylotype is immunologically active in mediating a protective effect against acne remains to be investigated. The work of Agak *et al*. provides however an indication thereof by demonstrating that only non-pathogenic *P. acnes* isolates found on healthy skin induced IL-10-secreting Th17 cells that were able to lyse *P. acnes in vitro* and, therefore, possibly participate in bacterial clearance *in vivo*.

While Th17 cells can be beneficial in clearing infection, excessive pro-inflammatory Th17 responses can be pathogenic. The findings of Agak *et al.* provide further evidence that Th17 cells are not always pathogenic. Indeed, Esplugues *et al*. previously demonstrated that excessive immune responses could be prevented by Th17 cells via IL-17-dependent upregulation of CCL20 in the gastro-intestinal tract (Esplugues et al., 2011). The *P. acnes* phylotype specific protective Th17 responses described by Agak *et al.* in this issue thus likely involve the immuno-modulatory effect of IL-10 and the microbicidal properties of Th17 cells.

The data of Agak *et al*. further suggest that in the skin, *P. acnes* plays a role in regulating the fate of Th17 to "Th17/Th1" differentiation programs, and the possible phenotypic plasticity in the late development of Th17 and Th1 cells. Th17 cells are known to display a high degree of plasticity driven by their environment (Muranski and Restifo, 2013). Th17 cells producing both IL-17 and IFNγ were first described in 2007 in patients with Crohn's disease and reported to result from a phenotypic shift of Th17 cells upon exposure to IL-12 (Annunziato et al., 2007). The microbial microenvironment is currently seen as an important factor in the development of Th17 or "Th17/Th1" responses, and fungi, not bacteria, specifically induce IL-12 secretion from antigen-presenting cells (APCs), resulting

in the phenotypic differentiation of fungus-specific Th17 cells towards the production of IL-17 and IFN^{3}. Indeed, in 2012, Zielinsky *et al.* reported that *Candida albicans* could induce IL-17^{+}/IFN-$^{3+}$/IL-10^{-} Th17 cells in an IL-12-dependent manner whereas *Staphylococcus aureus* induced Th17 cells to produce IL-10 (Zielinski et al., 2012). Interestingly, IL-1β was shown to be essential for *Candida albicans*-specific Th17 differentiation, whereas IL-1β inhibition promoted IL-10 production. The work of Agak *et al*. goes beyond the interesting field of distinct Th17 phenotypic properties regulated by bacteria and fungi demonstrating now that different strains (phylotypes) of a same bacteria may regulate the nature of Th17 responses. Thus, there is increasing evidence that such dichotomous Th17 responses largely depend on the local context and composition of the microbiome. The nature of the contextual commensal and/or pathogen and, amongst others, its ability to induce IL-12 and IL-1β or not may be key drivers of pathogenic or non-pathogenic Th17 responses (Figure 1). In such a context, the use of IL-1β inhibitors may rather favor IL-10-producing Th17 cells, described to be protective in certain situations (McGeachy et al., 2007), rather than fully inhibiting Th17 differentiation. Moreover, based on the report of Agak *et al*. one could hypothesize that the use of IL-17A inhibitors alone may also impair the protective function of Th17 cells and therefore not be specific enough to selectively treat the excessive inflammation characteristic of acne.

As reported in this issue, the findings from Agak *et al.* demonstrating *P. acnes* strain-dependent effects on the differentiation of Th17 subsets resulting in contrasting biological properties (pathogenic vs. protective) highlight the complexity of cutaneous microbiome/host interactions in skin health and disease.

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