Targeting T2 Inflammation by Dupilumab Impacts on the Microbiomic “Ménage à Trois” of Atopic Dermatitis

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Dupilumab leads to an improvement of the dysbiosis in lesional and non-lesional skin in atopic dermatitis (AD). Although the causal relationship between inflammation and dysbiosis remains unclear, strategies to normalize microbiome composition remain a relevant approach in AD. How and when to best individually impact on the microbiome to improve AD in the long-term and potentially modify disease is worthy of additional exploration.

Colonization of atopic dermatitis (AD) skin with Staphylococcus aureus was recognized in the 1970s (Aly et al., 1977) and variation during local treatment has been well documented (Stalder et al., 1994). In the last decade, this observation experienced a scientific revival secondary to high-throughput sequencing technologies in the context of the Human Microbiome Project (Byrd et al., 2018). However, although the concept of dysbiosis in AD and the correlation between S. aureus overgrowth and flares are well established, the causality issue remains unsolved.

Callewaert et al. (2020) report on microbiomic alterations observed during a phase 2 trial in moderate-to-severe patients with AD using the first in class biologic dupilumab. Although probably not of significant importance for the overall interpretation of the results, it should be noticed that in contrast to the approved regimen for dupilumab, in the present study there was no loading dose, and the weekly-applied dose was 200 mg instead of 300 mg. The key findings of this study are as follows: (i) during exposure to dupilumab, the microbial diversity increased and the abundance of S. aureus decreased both in lesional and non-lesional skin; (ii) these findings correlated with clinical improvement as measured by EASI and SCORAD; (iii) the decrease in S. aureus abundance correlated to the type 2 immunity biomarkers TARC/CCL17 and PARC/CCL18; (iv) the effect was lost 16 weeks after stopping the therapy. To understand the significance of these findings, it is important to place them in the context of the current knowledge on the microbiome in AD.

The skin microbiome interaction in a nutshell: A sensible “ménage à trois”

Unraveling the mechanisms regulating the composition of the skin microbiome resulting from the complex cross-talk with the skin immune system is key to understand whether S. aureus is a major player or only a bystander in the inflammatory reaction in AD, and how therapeutic approaches may have an impact on the microbiome. Briefly, this complex ecosystem can be compared to a kind of “ménage à trois,” (Figure 1) where commensals (the “good guys”) try to control the growth of potential pathogenic bacteria (the “bad guys”), while the skin immune system is providing the ecological niche that supports this battle. Quorum sensing mechanisms explain how the “good guys” control the growth of the “bad guys” (e.g., by antibiotic and lantibiotic peptides; Williams et al., 2019). In contrast, it is still not clear how the skin immune system can differentiate between “good guys” and “bad guys” to produce an adequate innate and adaptive response against the potential pathogenic agents, for example, via the production of antimicrobial peptides (AMP) and/or T helper type 17 effector cells, respectively, without harming the commensals. This sensible and well-balanced interaction, which includes an education of the adaptive immune system by the microbiome (Belkaid and Tamoutounour, 2016) via resident dendritic cells, can be disturbed from the host side by several mechanisms, such as a genetically-driven barrier dysfunction (e.g., FLG mutation) and/or local inflammatory reactions altering the barrier function and the antimicrobial properties of the epidermis (Howell et al., 2006). Lack of recognition of microbial signals by resident epidermal Langerhans cells may contribute to a defective adaptive immune response (Iwamoto et al., 2018). Taken together, these mechanisms may ultimately lead to loss of control by the skin immune system and to microbial dysbiosis.

Targeted therapy against T2 cytokines modulates the skin microbiome: Mechanistic aspects

Inflammation and T2 cytokines, which are released locally both by resident and invading inflammatory cells, have been reported to be detrimental for barrier function and AMP production. On the one hand, the overall reduction of the inflammation in the dermis and epidermis may have significantly altered the ecosystem and, more or less, selectively hampered the growth of S. aureus. On the other hand, because dupilumab blocks the binding of IL-4 and IL-13 to IL-4Rα, their multiple detrimental activities, particularly those of IL-13 (Bieber, 2019), on epidermal defense functions are

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inhibited. Therefore, the effect observed in this report was expected and is likely a dual, but indirect one. Whether or not the long-term use of dupilumab with better control of the condition has a more profound and sustained impact on the dysbiosis in AD remains to be investigated. In this context, it is noteworthy that in the phase 3 of the clinical development program of this drug, the risk for severe skin infections was reduced in patients treated with dupilumab compared with the placebo group (Eichenfield et al., 2019). This would support the concept that targeting T2 cytokines contributes to better long-term control of potentially pathogenic microbes in AD. As reported by Callewaert et al. (2020), in contrast to topical therapy, which typically only addresses lesional skin areas, a systemic approach targeting T2 cytokines also bears the substantial advantage that non-lesional skin, which harbors a similar dysbiosis as lesional skin, will have a benefit from this strategy. Considering that the subclinical inflammatory reaction present in non-lesional skin most likely provides a significant contribution to the overall inflammatory burden in AD and to its systemic character, targeted therapies aimed to control the T2-mediated inflammation may have a more profound effect on the fate of the disease as they improve the dysbiosis on the entire surface area.

It would be of great interest to explore whether dupilumab has a similar effect on the lung microbiome in asthma and in chronic rhinosinusitis with nasal polyps, where S. aureus has been suspected to play a crucial role (Teutelberger et al., 2019). Regarding the ongoing discussion on the role of S. aureus in the generation of the inflammatory reaction in the skin, the lack of sustainability of the effect induced by dupilumab after stopping the exposure to it suggests that S. aureus overgrowth should be considered a secondary effect and not a causative element, at least in adults where the study has been performed.

Perspectives: When would strategies aimed to modulate the microbiome in AD make sense?

Other non-mutually excluded hypotheses regarding the role of S. aureus in the pathophysiology of AD could also

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**Clinical Implications**

- Dysbiosis and T2 inflammation are important hallmarks of atopic dermatitis but it is still unclear which is the chicken and which is the egg.
- Targeting T2 cytokines with biologics, such as dupilumab, improves the diversity of the skin microbiome and reduces the colonization with *Staphylococcus aureus* in lesional and non-lesional skin.
- It remains to be determined how and when to best individually modify the skin microbiome to improve atopic dermatitis in the long-term and potentially modify disease.

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**Figure 1. The microbiome interaction with the skin immune system in a nutshell: A sensible “ménage à trois.”** (a) Commensal and potential pathogenic microbes together with cells of the skin immune system are in a constant cross-talk. In normal skin, commensals control the growth of pathogens by mechanisms of quorum sensing, and the production of AMPs by KCs contributes to control of the microbiome composition. KCs and epidermal LCs steadily sense signals from the commensals and potential pathogenic agents by, for example, TLRs. LCs continuously inform the adaptive immune system on possible variations of microbiome diversity, potentially leading to appropriate Th17 responses. (b) In contrast, in AD, T2 inflammatory reactions decrease the production of AMPs by the KCs, whereas the LCs are not able to sense the microbiomic signals, failing to initiate the adaptive immune response. This leads to a lack of control of the pathogens and, thus, to dysbiosis. AD, atopic dermatitis; AMP, antimicrobial peptide; KC, keratinocyte; LC, Langerhans cell; Th17, T helper type 17; TLR, Toll-like receptor.
be considered for future therapeutic strategies.

1. *S. aureus* plays a role in the very early phase of AD in infancy. Studies performed in newborns have shown that colonization with commensal *staphylococci* is associated with a lower risk of developing AD (Kennedy et al., 2017). Moreover, the overall microbiome is different in adult versus pediatric AD (Shi et al., 2016). Hence, one can speculate that *S. aureus* colonization plays significant roles in infancy and early childhood in inflammation, as well as mechanisms leading to sensitization (and production of IgE) through the epidermal compartment. Strategies that directly (e.g., by bleach baths or microbiome transplantation) or indirectly (e.g., by targeting T2 cytokines or other anti-inflammatory approaches) affect the microbiome may be more relevant in the pediatric population than in adults. Such strategies even have the potential for disease modification, considering that they would be able to impact on the mechanisms involved in the atopic march.

2. The composition of the microbiome reflects the type of genetic defect and/or inflammatory reaction underlying AD. Based on this assumption, it could be feasible to predict from the microbiomes, the kind of therapeutic approach that would best fit to overall control the underlying inflammation. The microbiome would then be considered as a kind of biomarker for new therapeutic approaches in AD.

3. *S. aureus* and their products generate and/or amplify inflammatory reactions only in a subgroup of children and adults with AD. The current prevention and therapeutic strategies, including those intended to modify the microbiome, are still designed in using a “one-size-fits-all” concept. However, the complex heterogeneity of the pathophysiology and clinical phenotypes in AD has recently been recognized. We are far from understanding whether *S. aureus* may preferentially play a role in a yet-to-be-defined subgroup of AD patients (children and adults) where the above mentioned direct or indirect strategies would be worthy of application. Programs that discover biomarkers for the stratification of AD will potentially enable stratification of the AD population concerning the role of *S. aureus* in disease pathogenesis.

In summary, the work of Callewaert et al. (2020) provides a new perspective on the impact of dupilumab, and potentially other drugs targeting T2 cytokines, on the skin microbiome. However, it remains to be explored how and when to best individually modify the skin microbiome in order to improve AD on a long-term and potentially disease-modifying basis.

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**CONFLICT OF INTEREST**
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**REFERENCES**