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STAPHYLOCOCCUS AUREUS AND THE SKIN MICROBIOME IN ATOPIC DERMATITIS

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SUMMARY

The knowledge accumulated in our understanding of atopic dermatitis has been acquired with progress in epidemiology, genomics and immunology. In this context, the reputed role of microbial organisms such as *Staphylococcus aureus* has always been regarded according to their pathogenic characteristics. More recently however, due to modern metagenomic analysis, it became evident that skin is colonized by a dense community of commensal microorganisms of which the diversity may be key for a normal skin. Thus, a new picture emerged, in which a balanced and diversified microbiome seems to engage in a dialogue with epithelial cells to control the growth of potential pathogens. In this context, the Toll-like receptor 2 (TLR2) seems to represent a pivotal structure for the recognition of microbial signals. TLR2 may also be critical for mounting an adequate Th17 driven antimicrobial response in the skin. Although we are just starting to explore und understand this complex interaction, it is speculated that a directed manipulation of the skin microbiome, aimed at restoring the default diversity could represent an interesting therapeutic approach

INTRODUCTION

Atopic dermatitis is a genetic complex disease, which display a highly complex phenotype (*Bieber*, 2008). In the recent years, progress in our understanding the pathophysiology of this disease has forwarded two main aspects, which seem to be mirrored by recent genetic inside. Indeed, on one hand this disease evolves on the background of an intrinsic epidermal barrier defect which is genetically determined (*Irvine* et al., 2011) and on the other hand is tightly related to a chronic inflammation (*Gittler* et al., 2013) emerging on the background of the so called atopic sensitization, i.e. IgE-mediated allergic reactions (*Wu* and *Zarrin*, 2014). From an immunological point of view, the initial Th1 versus Th2 dogma, which has dominated our understanding of the pathophysiology of atopic dermatitis, has more recently evolved in a more diverse landscape including the role of regulatory T-cells, Th22-cells and Th17-cells (*Eyerich* and *Novak*, 2013). The latter cells have been in the focus of our interest in the last years since they have been recognized as pivotal in immunity against *Staphylococcus aureus* (*Lee* et al., 2010; *Miller* and *Cho*, 2011). Indeed, this bacterium has been known since many years to be responsible for a substantial colonization of the involved as well as the uninvolved skin of atopic dermatitis (*Hauser* et al., 1985; *Boguniewicz*, 2012). Thus, although atopic skin is reproducibly heavily colonized by *S. aureus*, his real pathophysiological role remains elusive.

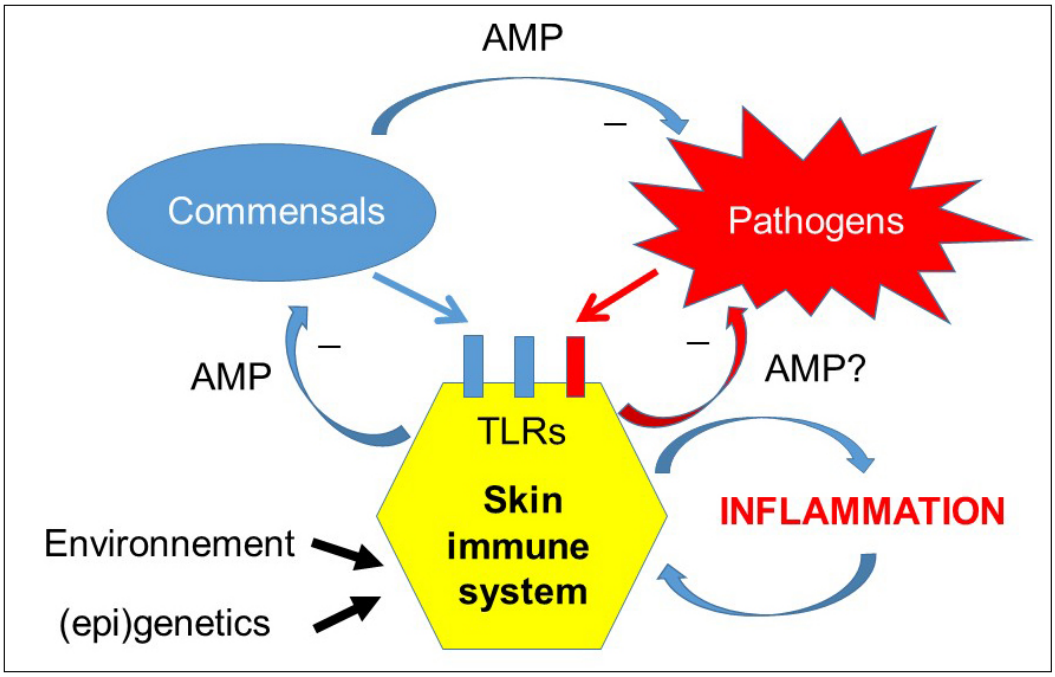

Figure 1: The cross-talk between the commensal, the putative pathogen bacteria and the skin immune system. The microbiomic balance on the skin: a good working "ménage à trois" (AMP = anti-microbial peptides; TLR = Toll-like receptors)

STAPHYLOCOCCUS AUREUS IN THE "PRE-MICROBIOMIC ERA"

So far, the observation of the colonization with *S. aureus* in atopic dermatitis has generated a number of hypotheses with regard to its potential pathophysiologic role in the initiation and maintenance of the chronic inflammation. Many in vitro and animal models have highlighted the numerous possible immunological impact points of *S. aureus* and their products on the skin immune system (*Higaki* et al., 1986; *Lever* et al., 1988; *Neuber* et al., 1991; *Hofer* et al., 1995; *Strange* et al., 1996; *Herz* et al., 1998; *Leung* et al., 1998; *Bunikowski* et al., 1999; *Morishita* et al., 1999; *Lin* et al., 2000; *Matsui* et al., 2000; *Zollner* et al., 2000; *Hikita* et al., 2002; *Matsui* and *Nishikawa*, 2002; *Wedi* et al., 2002; *Heaton* et al., 2003; *Lehmann* et al., 2004; *Breuer* et al., 2005; *Cardona* et al., 2006; *Langer* et al., 2007; *Machura* et al., 2008). Following mutually non-exclusive acting points have been identified so far: (i) polyclonal stimulation of T-cells (*Hemady* et al., 1983; *Skov* and *Baadsgaard*, 1995; *Strickland* et al., 1999), (ii) induction of *S. aureus*-specific IgE (*Walsh* et al., 1981; *Abramson* et al., 1982; *Henocq* et al., 1982; *Friedman* et al., 1985; *Nordvall* et al., 1992; *Bunikowski* et al., 1999; *Lin* et al., 2000; *Rossi* et al., 2004), (iii) induction of cytokines and chemokines from keratinocytes (*Vu* et al., 2010; *Takai* et al., 2014), (iv) induction of corticoid resistance by T-cells, (v) induction of homing receptor CLA on migrating T-cells in the skin (*Torres* et al., 1998).

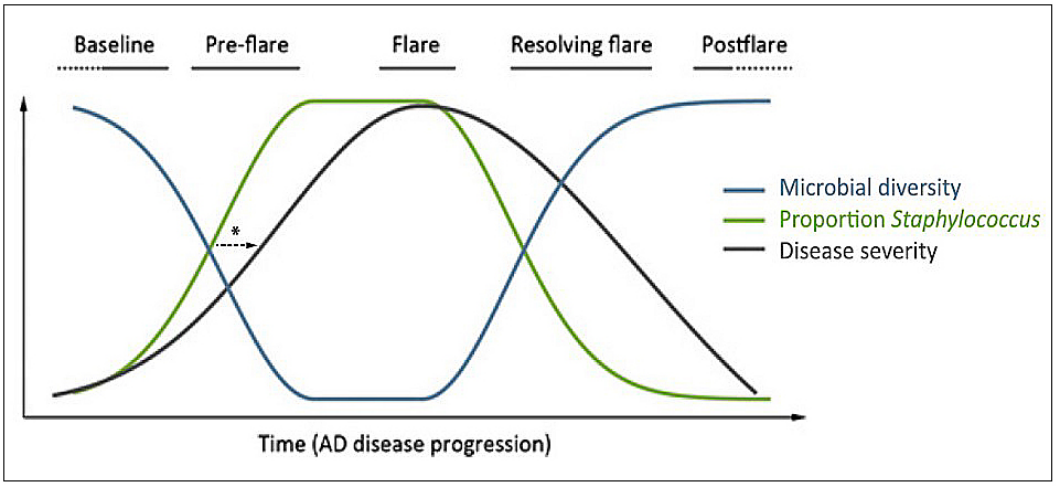

Figure 2: A putative temporal scenario of the microbiomic diversity and staphylococci growth with regard to the evolution of a flare in atopic dermatitis (from: Kong et al., 2012).

All these effects can act in concert to induce and possibly maintain a chronic inflammatory reaction in atopic skin. Moreover some *in vivo* experiments have shown that the application of *S. aureus* in patch test model on the skin of atopic dermatitis can induce an allergic reaction or inflammation similar to that observed in the disease itself (*Strange* et al., 1996; *Langer* et al., 2007). However, our view of the role of microbial agents on the skin was mainly dictated by the limited information provided through conventional technics in culturing skin-derived microbes. Indeed only one to 2% of the overall microbiomic colonization of the skin was evaluated by these conventional culture technologies.

STAPHYLOCOCCUS AUREUS IN THE "MICROBIOMIC ERA"

More recently, in the context of the human microbiome project (HMP), high throughput technologies based on 16 S RNA gene analysis have shown the tremendous diversity and a completely different picture of the microbiome resident in our body and on normal skin as well as the changes observed during different skin conditions (*Grice* et al., 2009; *Group* et al., 2009; *Costello* et al., 2009). Thus, a new picture emerges where the microbiome is now considered as an integral part of the epidermal barrier on the skin and the diversity of the microbiome seems to be key to understand the normal physiology and pathophysiology of this organ as well as for those of most other organs (*Kuo* et al., 2013a). To summarize this highly complex field of research, it can currently be postulated that normal skin is the product of a steady cross-talk between the skin immune system, the commensal microbes and the potentially pathogens on the skin, e.g. a kind of good working "ménage à trois" (*Zeeuwen* et al., 2012, 2013; *Nakatsuji* et al., 2013; *Grice*, 2014) (Figure 1). Thus, the high diversity of the skin microbiome seems to be key for a healthy skin. Most importantly, the so-called normal skin in

atopic dermatitis already harbours a reduced diversity of the microbiome, which is dominated by *S. aureus* as expected from the conventional culture technologies (*Kong* and *Segre*, 2012; *Kong* et al., 2012; *Oh* et al., 2012; *Chen* and *Tsao*, 2013). However, in the context of lesional skin, this altered diversity is even worsening and could precede the appearance of flares (*Kong* et al., 2012) (Figure 2). According to this hypothesis, the growth of *S. aureus* could indeed have a strong impact on the generation of flares and/or the perpetuation of chronic inflammation. However, we have completely underestimated the role of the other microbes present on the skin such as *Acinetobacter* or *Staphylococcus haemolyticus*. Indeed commensal microbes are in "steady dialog" with the potential pathogens and seem to control their growth by producing anti-microbial peptides. Among them, *Acinetobacter* also may display protecting effects against sensitization through the skin as well as allergic inflammation (*Fyhrquist* et al., 2014).

However, the reasons for this decreased diversity in the microbiome on normal looking and uninvolved atopic skin remains elusive. When considering the two main aspects in the pathophysiology of the disease, one may argue that the genetically driven intrinsic changes in the barrier function themselves could be pivotal for the overall changes in the microenvironment and favour the preferential growth of *S. aureus* under these conditions. This genetic control of the skin microbiome is most likely to that observed for the gut microbiome (*Goodrich* et al., 2014). On the other hand, it appears that in patients with atopic dermatitis, in contrast to other diseases such as psoriasis, an adequate Th17 response may be missing in the skin (*Toda* et al., 2003; *van Beelen* et al., 2007; *Eyerich* et al., 2009; *Auriemma* et al., 2013). Therefore, it can be speculated that the adaptive immune system in these individuals fails to shape and mount an efficient immune response against *S. aureus* (*Hayashida* et al., 2011). When considering the immune phenomenons underlying an appropriate Th17 response (*Miller* and *Cho*, 2011), recognition structures of the innate immune system such as Toll-like receptors (TLR) could play a key role in this context. Indeed, preliminary experiments in our group have shown that TLR2 is significantly downregulated on epidermal dendritic cells but not on keratinocytes in atopic individuals (*Iwamoto* et al., submitted). Moreover, these cells seem unresponsive to TLR2-ligands and are finally not able to induce a correct Th17 response. Whether this alteration in the dendritic cell biology is intrinsic to this lineage and/or the results of a peculiar microenvironment in the skin potentially induced by microbiomic signals is currently under investigation.

On the other hand, the possible role of TLR2 in atopic dermatitis has been highlighted many years ago in the context of single nuclear polymorphism of this structure reported in atopic individuals (*Prescott* et al., 2008; *Kormann* et al., 2009; *Oh* et al., 2009; *Liu* et al., 2011; *Potaczek* et al., 2011; *Fuertes* et al., 2013). Moreover, there are some conflicting results reported about the functionality of TLR2 expressed on keratinocytes or monocytes in patients suffering from atopic dermatitis (*Hasannejad* et al., 2007; *Sumegi* et al., 2007; *Niebuhr* et al., 2010; *Vu* et al., 2010; *Kuo* et al., 2013b; *Takai* et al., 2014). In any case, TLR2 has been recognized as a central recognition structure potentially involved in mechanisms leading to downregulation of atopic inflammation as shown in animal models.

CONCLUSION

Recent progress in our understanding of the microbiome on the skin in atopic dermatitis has substantially changed our view on the potential role of *S. aureus* in this condition. Moreover, the pivotal role of TLR2 on dendritic cells and their putative involvement in the induction of adequate Th17 response is now in the focus of our interest. Whether the microenvironment in atopic dermatitis provides a particular niche for the growth of *S. aureus* or inversely *S. aureus* induces a particular microenvironment in the skin of these patients remains unclear. Furthermore, the possibility that the microbiome on the skin has not only an impact on the immune system but also may display some impact on the epigenetic regulation in the skin has to be considered for our understanding on the natural history of this disease. Finally, there is growing evidence that the alteration of the diversity of the microbiome on the skin represents an interesting target for new approaches aimed at a manipulation and/or correction of the diversity, potentially associated with the use of microbiome-derived compounds able to prevent or to correct the sensitization and the chronic inflammation in these individuals.

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