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Canine and Human Atopic Dermatitis: Two Faces of the Same Host-Microbe Interaction

Domenico Santoro[1,3] and Aline Rodrigues Hoffmann[2,3]

Host-microbe interaction has been suggested to play a critical role in the pathogenesis of atopic dermatitis. The dog has been shown to be the best model to study both pathogenesis and microbiome modifications in atopic dermatitis. Bradley et al. show a significant correlation between microbiome diversity, clinical signs, and skin barrier function in atopic dogs before, during, and after antimicrobial therapy.

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Introduction

In recent years, several studies utilizing next generation sequencing have described the skin microbiome in humans. Healthy individuals are colonized with a diverse microbiota, with significant interpersonal variabilities, and differences across body sites in the same individual (Grice and Segre, 2011). Canine skin is no different, and it is colonized with an even more diverse microbiota, also with significant differences across individuals and body sites (Rodrigues Hoffmann et al., 2014). The microbiota diversity is reduced in both people and dogs with atopic dermatitis (AD). In addition, the role of beneficial bacteria, such as coagulase negative Staphylococci, has been largely demonstrated (Gallo, 2015). Furthermore, it is clear that the presence of pathogenic bacteria, such as *Staphylococcus aureus*, in people and *S. pseudintermedius* in dogs, may induce exacerbation/reactivation of the clinical signs of AD in people and dogs, respectively (Kong et al., 2012; Santoro et al., 2015; Williams and Gallo, 2015). However, the relationship between microbiome diversity, clinical signs, and skin barrier function after administration of systemic antimicrobial agents has not been completely elucidated. To elucidate this relationship, animal models that share the same environment with people would be extremely useful. Currently, mice have been used in large measure to study the specific genetic changes in AD (knockout technology); however, their use is limited, due to the absence of natural disease or clinical similarities with human AD (Santoro and Marsella, 2014). On the other hand, dogs are naturally affected by AD, they show clinical and immunological similarities with the human disease, and they share much of the same environment with their owners (Figure 1) (Santoro and Marsella, 2014). Thus, dogs with AD represent a perfect model to study host-microbiome interaction, mirroring the human AD. Bradley et al. (2016) confirmed the plasticity of the skin microbiome in dogs and how this changes in accordance with clinical signs, skin barrier function, and administration of antimicrobials. The authors have also shown that pathogenic Staphylococci (*S. pseudintermedius*) are more predominant in canine atopic skin (Bradley et al., 2016), as has been shown in atopic children (*S. aureus*) (Kong et al., 2012).

Microbiome and atopic dermatitis: human and canine

Bradley et al. (2016) report that dogs with flares of AD develop dysbiosis of their microbiota because of increases in relative proportions of the genus *Staphylococcus* (Figure 2). In this well illustrated study, the epidermal barrier functions and the microbiota of canine patients with AD and superficial pyoderma were analyzed during flares (and before antimicrobial treatment), 4–6 weeks after antimicrobial treatment, and another 4–6 weeks after therapy had been discontinued. During flares, these dogs had lower diversities of their microbiota in the pinna and axilla compared with control dogs. The reduced diversity correlated with increased relative abundances of *Staphylococcus spp.*, predominantly *S. pseudintermedius*, across all skin sites. Beta diversity differences were also observed between canine AD and healthy control dogs. After antimicrobial treatment, the relative abundances of *Staphylococcus spp.* were reduced and diversity was restored. However, after clinical resolution of the pyoderma and discontinuation of the antimicrobial therapy (for at least 1 month),

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Clinical Implications

- *Staphylococcus pseudintermedius* is the most abundant cutaneous pathogen in canine atopic dermatitis.
- The cutaneous microbiota normalizes after treatment with antimicrobial agents.
- Cutaneous microbiota diversity correlates with skin barrier function and clinical signs in atopic dermatitis.

microbiota diversity decreased again in atopic dogs. Severe canine AD was also correlated with impaired barrier function, with flares having lower transepidermal water loss and altered skin pH, confirming previous studies (Santoro et al., 2015; Zając et al., 2015).

The findings presented by Bradley et al. (2016) are quite similar to those found in a study by Kong et al. (2012), which demonstrated that children with AD have lower diversities in their microbiota and markedly increased relative abundances of *Staphylococcus* spp., especially *S. aureus*. This demonstrates that, similar to people, dogs with AD have dysbiosis of their microbiota, which is restored with antimicrobial therapy and the remission of their lesions. In the study developed by Kong et al. (2012), in children who received intermittent treatment, including topical and/or systemic anti-inflammatory drugs and/or antimicrobial therapy, diversity was maintained, similar to that of control

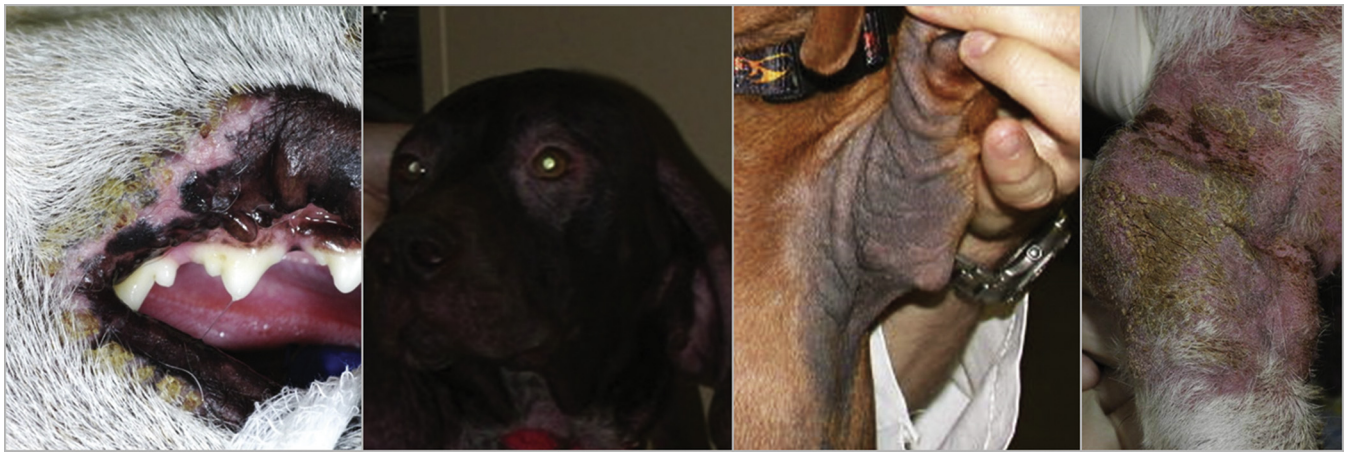

Figure 1. Canine atopic dermatitis: typical clinical features of naturally affected dogs with atopic dermatitis. The most commonly affected areas include face (perioral and periocular), axillae, and flexor cubital areas resembling human atopic dermatitis.

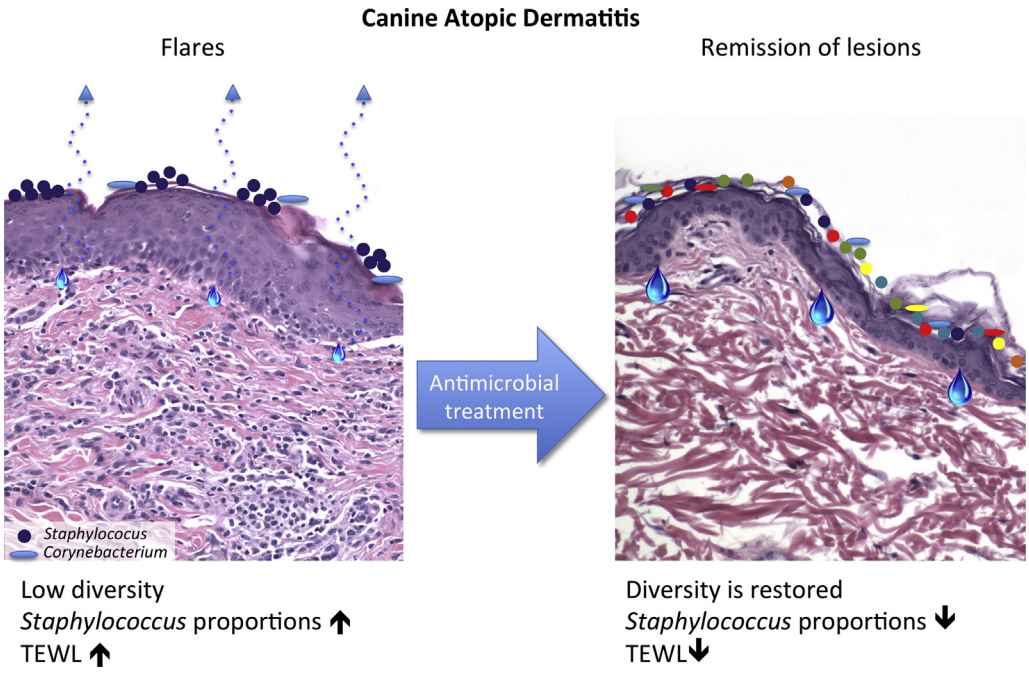

Figure 2. Canine atopic dermatitis during flares and remission of lesions. During flares, atopic dogs are presented with low microbial diversity, which is primarily due to increased relative abundances of *Staphylococcus spp.* Flares also result in increases in transepidermal water loss (TEWL). After antimicrobial therapy and during remission of lesions, TEWL is reduced, and diversity is restored in response to reductions in relative abundances of *Staphylococcus spp.*

individuals, and relative abundances of the genus *Staphylococcus* were reduced compared with the nontreatment group. These findings support use of therapies to revert microbial dysbiosis and for the remission of skin lesions in humans and animals, as well as demonstrating that dogs can serve as an excellent model to study therapeutic regimens that modulate the skin microbiome.

Furthermore, in a very recent study, Kobayashi et al. (2015), using Adam17DSox9 mice, demonstrated that *S. aureus* and *Corynebacterium bovis* are likely to contribute to eczematous inflammation in this mouse model. Bradley et al. (2016) reported that besides having relatively increased abundances of *Staphylococcus spp.*, the genus *Corynebacterium* was also found to be more abundant in the groin area during flares, compared with control dogs. On the other hand, relative abundances of *Corynebacterium spp.* decreased during flares in children with AD, with baseline and postflare skin having similarly increased relative abundances (Kong et al., 2012). These studies demonstrate that the cutaneous microbiota has complex relationships, and they highlight further the usefulness of dogs with AD as model to study the microbiota during and after flares of their disease.

Conclusions

This study enriches our knowledge about how the cutaneous microbiota varies in atopic dogs, before and after antimicrobial intervention. Bradley et al. (2016) have shown a strong correlation between dysbiosis of the cutaneous microbiota and altered skin barrier, measured via transepidermal water loss, pH, and stratum corneum hydration, in atopic dogs and how these parameters correlate with severity of the skin lesions in dogs. This work is not able to tell us whether changes in the microbiota are responsible for the atopic clinical signs or whether these are only a consequence of the cutaneous inflammation of atopic disease. It is also important to note that to date the relationship between the innate immune-defense (e.g., antimicrobial peptides, fatty acids, and keratinocytes) and microbiota remains unknown even though we do know that cutaneous innate immunity is altered in both humans and canine patients with atopic disease.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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