Immunology and pathogenesis of canine demodicosis

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Immunology and pathogenesis of canine demodicosis

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Demodex mites colonized the hair follicles and sebaceous glands of mammals millions of years ago and have remained relatively unchanged in this protected ecologic niche since then. The host immune system detects and tolerates their presence. Toll-like receptor-2 of keratinocytes has been demonstrated to recognize mite chitin and to elicit an innate immune response. The subsequent acquired immune response is poorly understood at present, but there is experimental and clinical evidence that this is the main mechanism in the control of mite proliferation. A transgenic mouse model (STAT-1−/−/CD28−/−) has demonstrated that the immune response is complex, probably involving both cellular and humoral mechanisms and requiring the role of co-stimulatory molecules (CD28).

It is known that a genetic predisposition for developing canine juvenile generalized demodicosis exists; however, the primary defect leading to the disease remains unknown. Once the mite proliferation is advanced, dogs show a phenotype that is similar to the T-cell exhaustion characterized by low interleukin-2 production and high interleukin-10 and transforming growth factor-β production by lymphocytes, as described in other viral and parasitic diseases.

Acaricidal treatment (macrocyclic lactones) decreases the antigenic load and reverses T-cell exhaustion, leading to a clinical cure. Although in recent years there have been significant advances in the management and understanding of this important and complex canine disease, more research in areas such as the aetiology of the genetic predisposition and the immune control of the mite populations is clearly needed.

Introduction

The management of canine demodicosis remains one of the main challenges in veterinary dermatology. The disease is highly prevalent in certain dog breeds and can be very severe, even leading to euthanasia of affected dogs.1–3 Treatment with macrocyclic lactones has provided a big step forward in the management of this condition; currently, long-term topical or systemic treatment with macrocyclic lactones is effective in most cases.4–7 However, veterinarians are faced with challenges in long-term treatment due to owner compliance and possible adverse events during therapy, particularly adverse effects in breeds with ABCB1 (formerly MDR1) gene mutation. Many aspects of the disease remain unknown, making prevention and management of some cases difficult.

One key question in the understanding of the disease is, why do some dogs develop generalized demodicosis at a very young age (juvenile demodicosis), a clinical presentation that is unique among mammals? According to textbooks, canine juvenile demodicosis is the consequence of a genetic defect that leads ultimately to defective control of Demodex populations by the host immune system.2,8 However, the mode of inheritance and the precise genetic defect or mutation remain to be elucidated. Also, the immune response and the mechanisms of control of Demodex populations in mammals have not been unravelled. The fact that Demodex mites cannot be cultured in vitro has been a major handicap in immunological investigation, because of the lack of availability of Demodex antigens. A second open question is, why, after treatment, does the disease usually not relapse? Certainly, clinical experience and scientific publications report that a majority of dogs do not relapse after an appropriately long treatment.2,6,7 However, this is in contrast to the theory of an underlying primary genetic cause, because the Demodex overgrowth and the skin lesions should reappear shortly after ceasing the acaricidal treatment.

It seems that only after reaching a more thorough understanding of the disease biology will it be possible to develop new and more effective strategies to prevent and manage canine demodicosis. The aim of this paper is therefore to review recent research concerning the genetics and immunology of canine demodicosis and their possible impacts on the management of the disease and on the whole disease model.

Demodex and mammals: an ancient relationship

Since the first description of Demodex mites in 1842 by the French dermatologist Gustav Simon,9 >140 known species or subspecies have been described, parasitizing...
hair follicles or sebaceous glands in 11 orders of mammals. Symbiotic associations between microorganisms and higher eukaryotes are common and range from mutualistic to commensal and parasitic. In the case of Demodex mites, some authors suggest that they should be considered as commensals, because they inhabit the pilosebaceous unit of mammalian skin and benefit from the human sebum in their sheltered ecological follicular niche. However, in humans and in other mammals a close link between Demodex infestation and skin diseases has been well documented. Canine demodicosis is probably the best and most important example of Demodex overgrowth-induced disease. In canine demodicosis, cutaneous inflammation is associated with excessive numbers of proliferating mites, including immature forms (eggs, larvae and nymphs), and the clinical cure is clearly associated with parasiticidal treatment and reduction in the number of Demodex mites. Therefore, Demodex mites are better considered as parasites that normally do not cause adverse effects on their host but that can act as opportunistic pathogens in certain circumstances.

Since the first description of Demodex in the 19th century, new Demodex species from very diverse mammals have been reported. This widespread occurrence of Demodex throughout the mammalian class suggests that the relationship is very ancient and that it was established at the beginning of the appearance of mammals on earth, when the first animals with hair follicles appeared. Anniotes, the ancestors of mammals, birds and reptiles, originated on islands in coal swamps over 300 million years ago, perhaps in pursuit of insects for food. For early anniotes, the adaptation to land from their amphibian ancestor was achieved by a major evolutionary innovation, i.e. the formation of the stratum corneum that prevented water loss from the skin and allowed them to move onto the land. Amniotes then evolved two different strategies to prevent water loss. In Sauropod amniotes, the ancestors of reptiles and birds, an α-keratinized layer formed above the β-keratinized layer and became the major constituent of scales and feathers. In Theropod amniotes, the ancestors of mammals, scales were lost and they developed protohairs, caused perhaps by a mutation leading to upregulation of a patterning trigger, such as β-catenin, that provided the necessary enhanced mechanical protection for the thin stratum corneum and also provided thermoregulation. It is estimated that hairs appeared over 210 million years ago.

The detection of Demodex antechinorum in a marsupial mouse, a species that when compared with eutherian demodicids is little modified, reinforces the idea that the mammal–Demodex relationship is very ancient. It is likely that the ancestors of both marsupials and eutherians already hosted ancestors of Demodex mites (100–200 million years ago). Eutherians did not diversify significantly until after the catastrophic extinction at the Cretaceous–Paleogene boundary, about 66 million years ago. At that time, their hair follicles probably hosted parasitic mites already. The host of the parasite subsequently passed through a long history of evolutionary change, but the parasite, located in a highly modified and evolutionarily sluggish niche (such as the hair follicle), remained relatively unchanged. Most probably, the genus Demodex forms an evolutionary clade and can be considered as a monophyletic group. In the Demodex genus, we have an extraordinary example of a remarkably long span of parasitic parallelism. Moreover, this long relationship between Demodex mites and mammals would explain the relative tolerance of the immune system of this parasite.

**Immunology of canine demodicosis**

**The control of Demodex populations**

As previously stated, most, if not all, mammals harbour Demodex mites in their hair follicles and sebaceous glands. The vast majority of hosts experience no adverse reaction from their presence, probably because the number of mites is maintained at a low level. In humans, the density of Demodex mites has been estimated at ≤5 mites/cm² on the facial skin using direct microscopic examination or skin surface biopsy. A mite density >5 mites/cm² is considered diagnostic of demodicosis, and in rosacea, mite density ranges from 5 to 60 mites/cm². There are no quantitative data about the density of mite populations in the dog. It seems, however, that the density is lower than in humans, although the mites in the dog spread all over the haired skin. This low mite density in the dog would explain why direct examination of plucked hairs usually does not reveal Demodex mites and why it is necessary to use highly sensitive techniques, such as real time-PCR, to detect Demodex DNA in dog skin.

According to most textbooks and authors, the immune system of the host is responsible for the control of mite populations. The host’s immune system appears to detect and tolerate the presence of these mites, and also has an inhibitory effect on mite proliferation and keeps mite numbers low without inducing an inflammatory response. There is some evidence that chitin can be recognized by Toll-like receptors (TLRs) from keratinocytes, especially by TLR2. A primary hypothesis is that Demodex mites are recognized by TLR2 from keratinocytes, eliciting an innate immune response. In fact, overexpression of TLR2 has been identified as one of the early key steps in human rosacea, and some authors have defined rosacea as a disease of...
TLRs and innate immunity mechanisms.\textsuperscript{35,36} However, there is a paucity of information concerning the subsequent steps of the immune response against \textit{Demodex}. The main antigens detected by the immune response, the type of specific immune response directed to the \textit{Demodex} mites and the effective mechanisms of control of the mite populations are almost entirely unknown. There are a few publications reporting that the host immune system detects lipase and some other proteases of the mites,\textsuperscript{37,38} although the relevance of this immune response remains to be analysed in more detail. The presence of specific anti-\textit{Demodex} humoral antibodies (of any subclass) has not been documented in the dog. Most investigations of the immune and inflammatory response against \textit{Demodex} mites have been carried out on humans with rosacea ( pityriasis rosacea or rosacea papulopustular) and most probably do not reflect the immune response of the healthy individual against normal \textit{Demodex} populations. As several authors have pointed out, the mechanism of the immune response and the control of \textit{Demodex} populations in the healthy dog is an area that needs enlightenment.\textsuperscript{15}

**Immunosuppression and demodicosis**

The assumption that the immune system plays a key role in the control of \textit{Demodex} mites originated from studies on clinical demodicosis. Three types of evidence support this assumption, as follows: (i) the possibility of inducing demodicosis by suppressing the immune response; (ii) the development of demodicosis in strains of immunodeficient mice; and (iii) numerous clinical observations of demodicosis in immunosuppressed people and animals.

Several research groups in the past have been able to induce demodicosis experimentally by immunosuppressing animals. Probably the best example is the classic experiment of Owen in 1972,\textsuperscript{39} who reported that eight puppies treated with antilymphocyte serum developed the generalized form of the disease, whereas five untreated littermates remained healthy. This finding, later confirmed by Healey and Gaafar,\textsuperscript{40} suggested that the depression of the host’s immunity preceded and was an important factor in the development of the generalized disease. These investigations are relatively old and understandably did not include detailed information on the cellular and molecular immune mechanisms leading to demodicosis.

Although it is supposed that healthy laboratory mice harbour \textit{Demodex} mites in their hair follicles, it is very difficult to find mites by performing skin scrapings or hair pluckings.\textsuperscript{41} However, several strains of immunodeficient mice that have greater numbers of \textit{Demodex} mites in the skin and hair follicles have been reported.\textsuperscript{42} An overgrowth of \textit{Demodex musculi} has been reported in SCID mice, CD3E transgenic mice (a strain lacking mature T lymphocytes and natural killer cells), and Prad1 transgenic mice, a strain overexpressing human cyclin D1 and manifesting severe thymic hyperplasia. A model of canine demodicosis in a SCID mouse engrafted with canine skin and infested with \textit{Demodex canis} has also been developed and proposed as a tool to investigate the pathogenesis of canine demodicosis.\textsuperscript{43}

Nevertheless, the best example of demodicosis in an immunodeficient mouse strain was the unexpected development of demodicosis (\textit{D. musculi}), with alopecia and severe dermatitis, in double-knockout mice lacking CD28 and STAT6.\textsuperscript{44} Interestingly, neither of the single-knockout siblings lacking either CD28 or STAT6 had increased numbers of \textit{Demodex} or skin lesions, even when they were housed in the same cages, indicating that control of \textit{Demodex} infestation is lost only when the functions of both molecules are inhibited. This is probably the most consistent and best-characterized experimental model of demodicosis reported so far. However, this double-knockout mouse strain was not developed to investigate the immunology of demodicosis but the immune response against an intestinal nematode (\textit{Nippostrongylus brasiliensis}), and little information about the immune response against \textit{Demodex} mites is given. From this model, it is, however, possible to conclude that immune control of \textit{Demodex} populations is very complex, involving many pathways, including humoral immunity (STAT6) and co-stimulatory molecules, such as CD28.

Finally, there are numerous reports of cases of demodicosis in immunosuppressed people and animals. Demodicosis has been reported, for instance, in patients with primary immunodeficiency,\textsuperscript{45} human immunodeficiency virus infection,\textsuperscript{46} renal transplant,\textsuperscript{47,48} haemodialysis\textsuperscript{49} and rheumatoid arthritis.\textsuperscript{50} Rosacea-like eruptions or demodicosis has also been reported after treatment with glucocorticoids,\textsuperscript{51,52} calcineurin inhibitors (tacrolimus, pimecrolimus),\textsuperscript{53,54} and epidermal growth factor receptor inhibitors.\textsuperscript{55}

There are also many case reports of demodicosis in animals with suspected or proven immunosuppression. \textit{Demodex cati} overgrowth has been diagnosed in cats infected with feline immunodeficiency virus, with diabetes mellitus and with squamous cell carcinoma.\textsuperscript{56,58} There are reports of demodicosis in dogs with leishmaniosis, hypothyroidism, hyperadrenocorticism and neoplasia, as well as in dogs undergoing immunosuppressive treatment for cancer or autoimmune diseases.\textsuperscript{2,59,60} Considering that not all dogs treated with corticosteroids or immunosuppressive drugs develop demodicosis, it is plausible to think that additional cofactors or a specific genetic profile are necessary for the development of clinical demodicosis.

Unfortunately, in most of these reports the immunosuppression was not investigated and the mechanisms leading to the overgrowth of the mite population remain unclear. Considering the great diversity of situations in which a \textit{Demodex} overgrowth has been described (from neoplasia to endocrine and metabolic disorders), it is very difficult to speculate about a common underlying pathomechanism. It seems that different types of immune dysfunctions can lead to the overgrowth of \textit{Demodex} mites in mammals. In some cases, it could be the specific inhibition of a pathway (e.g. after treatment with epidermal growth factor receptor inhibitors), while in others the demodicosis seems to be the consequence of inhibition of the normal functioning of several cell types (e.g. after glucocorticotherapy).
Immunosuppression in spontaneous canine demodicosis: T-cell exhaustion

Several research groups worldwide have investigated the immunological profile of dogs suffering from generalized demodicosis, with the aim of detecting key immunological abnormalities that could explain the pathogenesis of the disease. Table 1 summarizes the main immunological abnormalities reported. From these investigations, it is difficult to conclude what are the key immunological defects in dogs with spontaneous generalized demodicosis. Most research has been conducted in small groups of dogs, of different breeds and ages and with different clinical manifestations. It is therefore especially difficult to distinguish between immunological abnormalities that could be considered the trigger of the Demodex overgrowth and those that could be the consequence of the demodicosis itself and of the associated secondary infections. However, several investigations seem to indicate that dogs with generalized demodicosis suffer from an immune dysfunction that has been called T-cell exhaustion.

This process has been defined as an antigen-specific effector T-cell dysfunction characterized by a stepwise progressive loss of T-cell function.\textsuperscript{61} T-cell exhaustion was described initially in viral infections, but later it was documented in parasitic infections and even in malignancies.\textsuperscript{62–64} Although there are differences in the profiles of the T-cell exhaustion described in diverse diseases, the T-cell-exhausted phenotype is usually characterized by low production of supportive/stimulatory cytokines, such as interleukin (IL)-2 and IL-21, high levels of suppressive cytokines, such as IL-10 and transforming growth factor-β, and low numbers of circulating CD4+ lymphocytes.\textsuperscript{61,65–67} As almost all of these changes have been documented in dogs with generalized demodicosis, it is very likely that these dogs suffer from T-cell exhaustion. T-cell exhaustion would also provide a plausible explanation for the lack of relapse of generalized demodicosis after treatment with macrocyclic lactones. In T-cell exhaustion, the decrease in antigenic load, as occurs during the gradual resolution of infection, helps the exhausted T-cell population to regain polyfunctional activity.

### Table 1. Main immunological abnormalities reported in dogs with demodicosis

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Experiment</th>
<th>Importance and comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased response to intradermally injected PHA and Con A</td>
<td>Measurement of intradermal reaction to PHA and Con A in dogs with demodicosis and puppies of Doberman dogs from a breeder with high prevalence of GD</td>
<td>Impaired cell-mediated immunity. The changes seem to exist before the development of demodicosis</td>
<td>40,79</td>
</tr>
<tr>
<td>Decreased blastogenesis of peripheral lymphocytes when stimulated with Con A and PHA. Impaired CMI response appears 3–6 weeks after clinical signs of GD</td>
<td>Measurement of blastogenesis of blood lymphocytes stimulated with Con A and PHA from healthy beagle dogs (3) and from beagle dogs with LD (3) and GD (3)</td>
<td>Immunosuppression follows rather than precedes the clinical manifestations of GD</td>
<td>80,81</td>
</tr>
<tr>
<td>Decreased in vitro lymphocyte blastogenesis response. Fewer cells expressing IL-2 receptors and decreased IL-2 production compared with control dogs</td>
<td>Measurement of lymphocyte blastogenesis and of the expression of IL-2 and IL-2R in dogs with GD (10)</td>
<td>Immunosuppression is present in dogs with advanced GD</td>
<td>82</td>
</tr>
<tr>
<td>CD3+ and CD8+ lymphocytes predominate in skin lesions. Some B cells (CD21+) and plasma cells are also present</td>
<td>Immunohistochemical study of skin biopsies of dogs with demodicosis</td>
<td>In the active lesion, cytotoxic T cells (CD3+/CD8+) infiltrate the hair follicle wall (mural folliculitis)</td>
<td>65,70,71</td>
</tr>
<tr>
<td>Upregulation of T-helper-2 responses. Increased expression of IL-5 and TGF-β (GD)</td>
<td>Expression of cytokines by PBMC of healthy dogs (10) and of dogs with LD (9) and with GD (10)</td>
<td>Elevated IL-5 and TGF-β expression normalized after treatment. High TGF-β expression could be a marker of GD</td>
<td>83</td>
</tr>
<tr>
<td>Increase in peripheral CD8+ lymphocytes; decrease in CD4+ lymphocytes and in the CD4+/CD8+ ratio</td>
<td>Quantification of CD4+ and CD8+ cells in the blood of healthy dogs and of dogs with LD and with GD</td>
<td>Dogs with GD have lower numbers of CD4+ cells than dogs with LD. Suspected T-cell exhaustion</td>
<td>65–67</td>
</tr>
<tr>
<td>Increased premature apoptosis of PBL</td>
<td>Determination of apoptosis in peripheral cells by flow cytometry in dogs with LD (13) and GD (13)</td>
<td>Increased premature apoptosis of PBL may be implicated in the immunosuppression and in the unrestrained proliferation of Demodex canis mites</td>
<td>84</td>
</tr>
<tr>
<td>Higher IL-10 serum levels in dogs with recurring GD than in healthy dogs and those suffering the disease for the first time</td>
<td>Measurement of IL-10 in serum of dogs with GD (17) and healthy control animals (9)</td>
<td>High IL-10 levels in dogs with relapsing GD may suggest T-cell exhaustion</td>
<td>85</td>
</tr>
</tbody>
</table>

Abbreviations: CMI, cell-mediated immunity; Con A, concanavalin A; GD, generalized demodicosis; IL, interleukin; IL-2R, interleukin-2 receptor; LD, localized demodicosis; PBL, peripheral blood lymphocytes; PHA, phytohaemagglutinin A; PBMC, peripheral blood mononuclear cells; TGF-β, transforming growth factor-β.

Numbers in parentheses represent the number of animals included in the study.
attributes and more closely match typical memory T-cells. According to this perspective, the main function of acaricidal treatment would be to reduce the parasite load to reverse the T-cell exhaustion and thereby give the host immune system the opportunity to regain control of the mite proliferation.

Genetics of juvenile generalized canine demodicosis

Canine juvenile generalized demodicosis is considered to have a hereditary basis, although there is very little published evidence supporting this hypothesis. The presentation of the disease at an early age, in siblings and related dogs, and the increased prevalence in certain breeds all support a hereditary basis. The observed reduction of the frequency of the disease by withholding affected and carrier dogs from breeding programmes would also argue in favour of a genetic background for the development of disease. However, none of these observations per se can be considered conclusive of a genetic origin of the disease. To the best of our knowledge, only one genetic study has been published. The authors, reporting on Argentinian mastiffs and boxers (56 affected dogs and 60 breed-matched control animals), offer a statistically significant association between the phenotype ‘generalized juvenile demodicosis’ and certain microsatellite markers or DLA haplotypes (FH2202, FH2975 and FH2054). This is probably the most convincing published evidence of a genetic background for juvenile generalized canine demodicosis.

Additional genetic studies are clearly needed to advance understanding of the primary causes of canine demodicosis and to develop an effective prevention strategy. A large-scale genome-wide association study focused on some of the breeds with high prevalence of the disease, followed by the sequencing of genome candidate regions, could be a fruitful approach. Considering the epidemiological data and the genetic information obtained from the STAT−/−/CD28−/− knockout mouse model, a single gene responsible for the disease is not to be expected. One combination, or several, of genotypes that increase the probability of developing the disease phenotype, as described in other parasitic diseases (leishmaniosis), seems more likely.

Table 2. Main pathogenic mechanisms in demodicosis

<table>
<thead>
<tr>
<th>Pathomechanism</th>
<th>Characteristics</th>
<th>Clinical manifestation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous barrier rupture</td>
<td>● Erosion of epithelium by pre-or oral styles and mouthparts</td>
<td>● Comedones</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>● Mechanical dilatation and rupture of hair follicles due to mite overpopulation</td>
<td>● Follicular papules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Effects of proteases from salivary gland</td>
<td>● Alopecia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Injury of keratinocytes by T cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>● Mural folliculitis due to immune reaction against Demodex antigen</td>
<td>● Erythema</td>
<td>65,70,71</td>
</tr>
<tr>
<td></td>
<td>● Granulomatous dermatitis against Demodex mites and hair fragments</td>
<td>● Follicular papules and pustules</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Alopecia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Granulomas present in the resolving phase of the disease</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity reaction (type IV)</td>
<td>● T helper cells around hair follicles and mites (human rosea)</td>
<td>● Erythema</td>
<td>65,70–72</td>
</tr>
<tr>
<td></td>
<td>● T cytotoxic lymphocytes (CD3+/CD8+) around and in the wall of hair follicles (canine generalized demodicosis)</td>
<td>● Follicular papules and pustules</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Alopecia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Pruritus</td>
<td></td>
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<tr>
<td>Secondary bacterial infection</td>
<td>● Leading to suppurative folliculitis–furunculosis</td>
<td>● Deep pyoderma (pustules, crusts and fistulous tracts)</td>
<td>2,71,79</td>
</tr>
<tr>
<td></td>
<td>● In humans, a hypersensitivity reaction against bacterial antigens has been described</td>
<td>● Erythema, pruritus</td>
<td></td>
</tr>
</tbody>
</table>
human rosacea, the T-helper lymphocytes (CD4+, T-helper-17) have been identified as the main inflammatory cells present in the perifollicular and dermal inflammatory infiltrates. In the dog, the cells have been reported to be CD3+ and CD8+ T lymphocytes, and they are considered to be cytotoxic T cells, which may mediate the injury in the follicular epithelium. Once in the dermis, the released mites, together with hair fragments and keratin, induce a granulomatous reaction, with a variable degree of lymphocytic infiltrates. The granulomas have been associated with the resolution phase of the disease, when the clinical lesions regress. The presence of a strong hypersensitivity reaction against the mites has been documented in papulopustular rosacea. A similar hypersensitivity reaction to the mites has not been documented in the dog, but the presence of CD8+ lymphocytes in the inflammatory infiltrate could be an aberrant or exaggerated immune response to the mites or against keratinocytes and Langerhans cells presenting Demodex antigens.

It has been demonstrated that Demodex mites can contain, transport and interact with bacteria of the cutaneous microbiome. In consequence, some of the lesions observed in demodicosis have been attributed to the interaction between Demodex and bacteria. In human rosacea, it has been demonstrated that Demodex overgrowth induces a proliferation of Staphylococcus epidermidis, which can lead to a skin infection, and a hypersensitivity reaction against bacterial antigens (Bacillus oleronius). According to these authors, bacterial proteins and antigens would be responsible for the inflammatory and vascular changes characteristic of rosacea.

In the dog, the association of Demodicosis with pyoderma is well established and is probably the most severe consequence of demodicosis. Treatment with antibiotics is prescribed if the clinical signs or cytological examination of exudates are suggestive of pyoderma. However, it is not known whether, as in humans, Demodex mites induce a proliferation of Staphylococcus pseudintermedius, or rather if this bacteria simply takes advantage of the epidermal barrier rupture that occurs in canine demodicosis. Although some recent papers have questioned the importance of the bacterial infection in canine demodicosis, it would probably be helpful to investigate the changes in the skin microbiome associated with canine generalized demodicosis.

Concluding remarks

In the course of evolution, Demodex mites have shown a long parasitic parallelism with their mammalian hosts. The host’s immune system appears to detect and tolerate the presence of these mites and also has an inhibitory effect on mite proliferation. There is some evidence that chitin can be recognized by TLRs from keratinocytes; however, the exact immunological mechanism that controls mite populations in dogs is still unknown. The initial cause of the mite overgrowth in juvenile generalized canine demodicosis is also unknown. Preliminary genetic studies have detected an association of the disease phenotype with certain haplotypes, but more extensive genetic studies are clearly needed. Once the disease has developed in a dog, indicators of T-cell exhaustion, such as the low production of supportive/stimulatory cytokines (IL-2 and IL-21) and high levels of suppressive cytokines (IL-10 and transforming growth factor-β) along with low numbers of circulating CD4+ lymphocytes have been documented. Up to this point, our understanding of the disease biology is still limited. Future research should focus on the control of mite populations by the immune system, the initial cause of the mite overgrowth, and the genetic background and inheritance of canine juvenile generalized demodicosis.

References


Résumé – Les Demodex ont colonisé les follicules pileux et les glandes sébacées des mammifères il y a des millions d’années et restent depuis, presque inchangés dans cette niche écologique protégée. Le système immunitaire de l’hôte détecte et tolère leur présence. Il a été montré que le récepteur Toll-like 2 des kératinocytes reconnait la chitine des acariens et entraîne une réponse immunitaire innée. La réponse immunitaire acquise qui en découle est peu comprise aujourd’hui mais il existe des preuves expérimentales et cliniques qu’il s’agit du principal mécanisme de contrôle de la prolifération des acariens. Un modèle de souris transgéniques (STAT-1/CD28) a démontré que la réponse immunitaire est complexe et implique probablement des mécanismes à la fois cellulaire et humoral et nécessite les molécules de co-stimulation (CD28). On sait que la prédisposition génétique à développer une démodécie juvénile généralisée existe. Cependant, le défaut primaire entrainant le développement de la maladie reste inconnu. Une fois que la prolifération des acariens est initiée, les chiens montrent un phénotype des cellules T semblable à d’autres maladies virales ou parasitaires caractérisée par une production lymphocytaire faible d’interleukine 2 et élevée d’interleukine 10 et de TGF-β. Le traitement acaricide (laclonate macrocyclic) diminue la charge antigénique et renverse l’épissage des cellules T menant à la guérison clinique. Bien que ces dernières années, de sérieuses avancées aient été faites dans la gestion et la compréhension de cette importante et complexe maladie canine, davantage de recherches sur l’étiologie de la prédisposition génétique et le contrôle immunitaire de la population d’acariens est clairement nécessaire.

Resumen – Los ácaros Demodex colonizaron los foliculos pilosos y las glándulas sebáceas de los mamíferos hace millones de años y han permanecido relativamente sin cambios en este nicho ecológico protegido desde entonces. El sistema inmune del hospedador detecta y tolera su presencia. Los receptores de tipo II similares a Toll en los queratinocitos han demostrado reconocer la quitina de los ácaros e iniciar una respuesta inmune innata. La siguiente respuesta inmune adquirida está poco caracterizada hasta el presente, aunque hay evidencia clínica y experimental que es el principal mecanismo de control de la proliferación de los ácaros. Un modelo transgénico en ratón (STAT-1/CD28) ha demostrado que la respuesta inmune es compleja y, probablemente implica tanto mecanismos celulares como humorales y requiere el papel de moléculas coestimuladoras (CD28). Se sabe que hay una predisposición genética a desarrollar una demodicosis juvenil generalizada, sin embargo el defecto primario que lleva esta enfermedad aún se desconoce. Una vez que la proliferación de los ácaros está avanzada, los perros muestran un fenotipo que es similar a agotamiento de los linfocitos T caracterizado por una baja producción de interleuquina 2, y la alta producción de interleuquina 10 y del factor de crecimiento transformante β por los linfocitos, tal y como se escribe en otras enfermedades víricas y parasitarias. El tratamiento acaricida (laclonate macrocíclicos) disminuye la carga antigénica e invierte el agotamiento de los linfocitos T, llevando a la curación clínica. Aunque en años
recientes ha habido avances significativos en el manejo y el entendimiento de esta importante y compleja enfermedad canina, se necesita más investigación en áreas como la etiología de la expresión genética y el control inmunitorio de la población de ácaros.