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Review Article

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Comparison of Canine and Human Immune System Response to Demodicosis

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Abstract

One of the types of external human parasites is a follicular scab called Demodex. Demodicosis is a skin disease in human and canine.The host body immune system is responsible for controlling the population of parasites and Disruption of the cutaneous barrier causes stimulation of Toll-like receptors (TLRs) Consequently, Demodex chitin detect by keratinocyte TLRs. According to the results, association between Demodicosis and the HLA gene showed that individuals with the gene HLACW2 are five times more likely to develop Demodicosis than others because Nk2 and T1 cells of the adaptive immune response are reduced. In human Demodicosis, factors such as carbohydrate-like Tn antigen (expressed by Demodex) and secretion of pro-inflammatory mediators may play a role in the innate immune response. Additionally, the expression level of TLR2 was increased and TLR4, TLR6 expression was decreased. Flow cytometry analysis of blood samples collected from individuals with human Demodicosis and healthy individuals showed that in the patient group, there were more T9 and T reg cells in the blood samples and in skin homing T cell populations compared to the control group. Studies of canine Demodicosis have reported that lymphocyte populations are composed mostly of CD3+ and CD8+ T cells. The importance of the humoral immune response during primary Demodicosis has not yet been determined because no significant differences in circulatory immune were seen. It seems that the host immune system appears to recognize and tolerate the presence of these mites, although the physiological role of this mite in healthy skin remains unclear.

Keywords: Demodicosis, Canine, Human, Immune System and Skin Health

1. Introduction

Ectoparasites are of great medical and veterinary importance [1]. One of the types of external human parasites is a follicular scab called Demodex which their life cycle is approximately 14–18 days from the egg to the larval stage, and finally, they reach the adult stage in 5 days [2,3]. Demodicosis is a chronic skin disease caused by follicular mites; among those that can cause disease in humans are Demodex Folliculorum and Demodex Brevis which cause chronic blepharitis and facial eruptions in both immune-competent and immune-deficient patients [4,5]. Canine Demodicosis is mainly categorized into localized and generalized forms due to their skin lesions distribution on different parts of the body. The majority of the cases with localized form have a good prognosis because of the spontaneous clinical recovery [6].

Demodex mites feed on the epithelial cells of the hair follicle or sebaceous gland. Mites are generally found on and around the face, especially in the forehead, cheeks, nose, and creases, but can sometimes be found in other parts of the body [7]. However, it seems that only susceptible individuals develop symptoms of mites, and between 11.9% and 72% of people are asymptomatic carriers of these mites. Studies have shown that the cellular immune response plays a vital role in the pathogenesis of Demodex parasite infection, which in turn, increases the incidence of Demodicosis in immunosuppressed persons, such as those with Acquired immunodeficiency syndrome (AIDS) and patients who are receiving immunosuppressive drugs [8,9]. Demodicosis is common in domestic dogs and cats. In dogs with this mite, symptoms such as red pimples on the skin, excessive hair loss, and itching of the skin around the eyes, face and legs can be seen. They are also involved in forming pustules in the corners of the mouth and dermatitis around the mouth and can even cause blepharitis caused by mental problems and stress [10-12]. One of the main challenges in veterinary medicine is the management of Demodicosis, especially in certain breeds of dogs, which can be very dangerous and even lead to euthanasia [13-15].

The recommended treatment for demodicosis varies depending on the type of sickness. For mild localized demodicosis, treatment may not be necessary as it often resolves on its own. However,

for generalized and complicated demodicosis with secondary infections, the treatment can be challenging and time-consuming. Dogs with demodicosis usually do not require systemic antibiotics unless there is a severe bacterial infection present. It is important to avoid using local or systemic corticosteroids, progestogens, or immunosuppressive agents in the treatment of demodicosis, if possible. These agents can inhibit the host immune system's ability to heal and may cause relapses or prevent them from occurring [16] .However, veterinarians have challenges in the long-term treatment of dogs. These include keeping the owner satisfied and possible side effects, especially in breeds with the ABCB1 (formerly MDR1) denomination. Many aspects of the disease remain unknown, making it difficult to treat and manage in some cases. It has always been an essential question to show symptoms by very young dogs in the face of Demodicosis, which Reference books have proposed genetic defects in the immune response to this disease [17].

In humans, the presence of Demodex spp can lead to the development of many skin and eye diseases, even when no symptoms are present[18]. Demodicosis in humans who do not have immunodeficiency diseases has several diagnostic criteria, including (i) the absence of pre-existing or concomitant inflammatory dermatitis, such as acne or rosacea; (ii) an abnormal increase in the number of Demodex after the test Active skin lesions at the time of examination (iii) Recovery of the disease only after adequate topical or systemic treatment with acaricides, but antibiotics with anti-inflammatory effects such as tetracycline or doxycycline or macrolides should not be used. In addition, due to the limited number of studies, it is now considered abnormal to observe more than 5 Demodex per square centimeter in standard skin surface sampling [19,20]. Forton and Maertelaer suggested that close interactions may exist between the Demodex mite, sebaceous gland size and function, and subtle variations in immunity, such as hypothyroidism [21].

Clinical signs of Demodicosis include (i) Absence of pre-existing or concomitant inflammatory dermatitis, such as acne (ii) Abnormal increase in the number of Demodex after the test of active skin lesions at the time of examination (iii) The lesions are usually irregular and asymmetric and are seen as satellite lesions (Iv) Lesions are follicular (v) are usually asymptomatic or with mild itching, and patients usually have no rosacea manifestations, such as erythema, transient flushing or telangiectasia [19].

Human-animal demodeciosis infections have been reported in some cases where the rare cases reported are still reliable due to reports of Demodex Canis and Demodex Folliculorum polymorphs [22-24]. The information available on the Demodex mite genome is incomplete due to its inability to be cultured in vitro and genome extraction problems due to chitin structures. Demodex in dogs is classified into Demodex Canis and Demodex Injai [25]. They were classified using the 16S mitochondrial genome (mtDNA) [26]. On the other hand, studies have been proposed to classify Demodex in the human species based on 16 S and cox1, in which mites are subdivided into D Folliculorum and D Brevis. Different classification methods based on 12S mtDNA regions, cox1-5', and the process of studying the DNA of their ribosomes are still ongoing [27].

Studies on different skin pathologies have shown an association between the immune system and human leukocyte antigen (HLA) in the development of pathological skin processes. Nevertheless, the role of HLA class I in the presentation of mite antigens is known. Studies investigated an association between the frequency of HLA Cw2 and Cw4 haplotypes and Demodicosis. In addition, an association between Cw2 and Cw4 alleles in the phenotype of patients with Demodex and a decrease in the number of natural killer (NK) cells was found [8].

This study aimed to review our understanding of immune system response in humans and dogs infected with Demodex by documenting the recent results on both human and canine Demodicosis, one of the best studied mite-associated animal cutaneous disorders.

2. Canine Demodicosis

2.1. Mechanism of Immune System Response

The host body system is responsible for controlling the population of parasites, and it seems that the host immune system tracks the parasites. In addition, it has an inhibitory effect on the multiplication of parasites and keeps the number of parasites low without causing inflammation [7,20]. Disruption of the cutaneous barrier causes stimulation of Toll-like receptors (TLRs). Consequently, the host immune system is exposed to Demodex antigens during the decay of mites. In addition, over-proliferation of Demodex mites can damage the hair follicle wall, and the chitin present in the mite's exoskeleton can be detected by keratinocyte TLRs, especially TLR2s [28]. Overexpression of TLR2 is known to be associated with rosacea [6,29].

In canines, Demodicosis manipulation of TLRs expression has been proposed. Significantly elevated expression of TLR2 and reduced expression levels of TLR4 and TLR6 in the peripheral blood mononuclear cells (PBMCs) have been documented in dogs with Demodicosis [6,27]. The proposed mechanisms for the development of canine demodicosis have focused on T cell exhaustion and inflammation-modulating cytokines. Individuals with demodicosis have shown a cytokine phenotype characterized by reduced production of stimulatory cytokines, such as interleukin (IL)-2 and IL-21. They also exhibit high levels of suppressive or immune-modulating cytokines, such as IL-10 and transforming growth factor β (TGFβ), along with low numbers of circulating CD4+ lymphocytes. These findings collectively suggest T cell exhaustion in dogs with demodicosis [30].

Activation of toll-like receptor 2 (TLR2) is known to increase IL-10 expression. Studies have shown that Demodex spp. leads to a significant increase in TLR2 expression and activity on keratinocytes [30,31]. IL-10 has several immune-modulating effects: (1) inhibiting Major Histocompatibility Complex (MHC) class II and co-stimulatory molecule expression on monocytes

and macrophages, and limiting the production of proinflammatory cytokines and chemokines; (2) directly acting on CD4+ T cells, thereby inhibiting their proliferation and production of IL-2, IFNγ, IL-4, IL-5 and tumor necrosis factor-alpha (TNFα); and (3) directly regulating innate and adaptive Th1 and Th2 responses by limiting T cell activation [30].

However, little information is available on the next steps of the immune response against Demodex, and the specific type of immune response to Demodex parasites and the practical mechanisms for controlling the parasite population is almost entirely unknown. However, based on the findings, the host immune system detects the parasite's lipases and some other proteases [32,33].

2.2. Immunosuppression and Demodicosis

The hypothesis that the immune system plays a role in controlling the Demodex parasite stems from clinical studies on Demodicosis. Evidence to support this hypothesis is: (1) the possibility of inducing Demodicosis by suppressing the immune system; (2) Development of Demodicosis in immunocompromised mice, (3) and multiple clinical observations of Demodicosis in immunocompromised animals [34]. Demodex population safety control is complex because it depends on many pathways, including humoral immunity (STAT6) and co-stimulatory molecules, such as CD28. There have been reports of Demodicosis in dogs with leishmaniosis, hypothyroidism, hyperadrenocorticism, neoplasia, and also, dogs undergoing immunosuppression due to having cancer or autoimmune diseases. Since Demodicosis has not been observed in all dogs treated with corticosteroids or immunosuppressive drugs, Additional cofactors or specific genetic profiles are thought to be required to develop the clinical form of Demodicosis. Different types of immune disorders appear to lead to the overgrowth of Demodex parasites in mammals, which in some cases can be because of specific inhibition of a pathway or the result of inhibition of the normal function of several cell types [17].

Numerous studies have shown that dogs with general Demodicosis suffer from an immune dysfunction that causes T cell fatigue. This process is a dysfunction of a specific T cell antigen characterized by a gradual decrease in T cell function. Exhausted T cells with low production of supportive/stimulatory cytokines, such as Interleukins (IL)-2 and IL-21 are usually characterized by high levels of suppressive cytokines, such as IL-10 and high levels of the beta-growth factor, and also, low circulating CD4+ lymphocytes. Exhausted T cells provide plausible evidence that general Demodicosis does not become acute after treatment with macrocyclic lactones. In T cell depletion, a reduction in antigenic load (as occurs when infection gradually clears up) helps the tired T cell population to become more compatible with normal memory cells in addition to regenerating multifunctional features [35-37]. Despite the very little published evidence, general Demodicosis of young dogs is inherited and the presentation of the disease at an early age, in siblings and dependent dogs, and the higher prevalence in some breeds based on heredity is a reason for this claim [14,38].

2.3. Pathogenesis of Demodex in Canine

Probably the importance of each mechanism from one species to another one, and in various clinical types of Demodicosis is different, but the most important suggested mechanisms for the pathogenesis of Demodex are:

•1. Rupture of the cutaneous barrier, which includes symptoms such as argon in the epithelium, mechanical dilation and rupture of hair follicles due to the accumulation of parasites, and protease damaged by T lymphocytes.

• 2. Inflammation associated with granulomatous dermatitis and folliculitis.

• 3. Type IV hypersensitivity, which is characterized by the accumulation of helper T lymphocytes and the accumulation of cytotoxic T lymphocytes around the hair follicles, especially in general Demodicosis of dogs.

• 4. Secondary bacterial infection that causes folliculitis and furunculosis.

Damage to the skin barrier caused by physical and chemical factors seems to be common and seen in different types of Demodicosis and in different species. Inflammatory reaction facilitates the rupture of hair follicles, which is associated with damage to keratinocytes in dogs [17]. According to the results, cytotoxic T lymphocytes that are involved in causing damage to the follicular epithelium are CD3+ and CD8+. Hypersensitivity to Rosacea disease in humans has not been reported in dogs, but the presence of CD8 + in inflammatory fluids can be considered a severe immune reaction in dogs [17,36]. The association between Demodicosis and pyoderma in dogs has been well established and is probably the most severe consequence of Demodicosis. If you observe pyoderma discharge in clinical signs, antibiotics may be the appropriate treatment. However, it is not yet clear whether, like what we see in humans, Demodex parasites in dogs cause Staphylococcus pseudintermedius to multiply or whether these bacteria can easily benefit from the rupture of the epidermal barrier that occurs in canine Demodicosis. Recent articles have questioned the importance of bacterial infection in canine Demodicosis [14,39,40].

3. Human Demodicosis

3.1. Human Immune System

The skin immune system is made up of several types of innate immune cells and compatible immune cells that are actually located in two layers of skin, the epidermis and the dermis. In addition to immune cells in the skin, pathogens can be detected by pattern recognition receptors expressed by non-immune cells. These cells participate in the immune response by releasing soluble mediators. By releasing sebum, the sebaceous glands prevent microbes from entering deeper layers and actually act as a "seal" for hair follicles [41,42]. Recently, it has been suggested that sebaceous glands play a role in skin immunity by producing antimicrobial peptides and secreting and producing chemokines and cytokines [43,44].

When a human is infected with Demodex spp., the immune system is activated with the help of Toll-like receptors (TLR). It is believed that a certain component of the Demodex chitin triggers

the pro-inflammatory response of keratinocytes through TLR-2 [18]. Inflammation of the skin is associated with the presence of immune cells, such as T cells, neutrophils, and monocytes in the skin. After the inflammation heals, some of these activated T cells leave the tissue, but others remain and become memory T cells [45-47]. Recent data point to the importance of B cells in skin immunity among lymphocyte populations during chronic inflammatory skin diseases. According to the results, they have pro-inflammatory and immune-regulating reactions, and unlike T cells, B cells are rarely present in healthy skin tissues [48].

According to the results of flow cytometry analysis in the group of patients with Demodex, the amount of CD3+ CD4+ T cells increased, while the level of CD3+ cells remained unchanged. After measuring the penetration of CD3 + and CD3+ CD4+ T cells into the skin and their placement in the skin by CLA as a skin-homing marker, it was concluded that CD3 + CLA + remained stable while CD3+ CD4+ CLA+ T cells increased compared to the control group(49). In comparison between the CD4+ T cell subpopulation subspecies and the control group by the flow cytometry evaluation, the results stated that the levels of TH9 and regulatory T (Treg) cells increased in patients with Demodex. Also, in the replacement test of CD4+ T-cell subpopulation in the skin with the association of CLA, an increase in TH9 and Treg cells was seen in demodex patients compared to the control group [49].

In the research conducted by OE AKILOV and colleagues, which compared the immune cells between people with demodex and healthy people, it was seen that the phagocytic cells and the complement system remained unchanged and the ratio of lymphocytes to monocytes in infected people is 3 times that of healthy people, and a significant decrease in the amount of CD16+ T cells has been seen. According to the results, mite density has a negative correlation with NK cells and CD95+ cells(7).

3.2. Pathogenesis

The mechanism of pathogenesis in humans is somewhat obscure, and the critical point in this issue is how the disease rotates from non-inflammatory to inflammatory. It is not known whether cystic or cutaneous Demodicosis is more likely to be caused by a host immune response or by large amounts of Demodex parasites. The key to clarifying the relationship between skin innate immunity and microbial homeostasis is the identification of cathelicidin LL-37 and the differential expression of cytokines produced and proteins present in inflammation [50,51].

Observations made on human scabies infection can help us to some extent to understand how parasites escape from the immune system or suppress immunity [52,53]. First of all, it should be noted that all three pathways of the complement system (classical, lectin and alternative) can be inhibited by 'scabies mite-inactivated serine protease paralogues' and 'serine protease inhibitors'. In a simulated model of human skin, in scabies disease, genes related to the expression of IL-1a, IL-1b, macrophage granulocyte colony-stimulating factor, and Granulocyte colony-stimulating factor, as well as genes involved in epithelial development and keratinization, are significantly regulated. In crusted skin scabies, the features of a polarized supplemental reaction (Th) are associated with a severe eosinophilic reaction and the penetration of CD8+ T cells into the dermis. In normal galls, a protective Th1 immune response is observed in favor of interferon c with the infiltration of CD4+ T cells into skin lesions [19].

3.3. Role of HLA A2 and CW2

Genetic background is an important risk factor for human Demodicosis. Patients with HLA CW2 and HLA CW4 human leukocyte antigen phenotypes are susceptible to Demodex over-proliferation because Nk2 and T1 cells of the adaptive immune response are reduced [3]. The results of the study of the association between Demodicosis and the HLA gene showed that individuals with the gene HLACW2 are five times more likely to develop Demodicosis than others. This ratio is 3.1 times higher in individuals with the HLACW4 gene than in healthy people. Interestingly, individuals with the HLA A2 gene are 2.9 times more resistant to Demodex than healthy individuals, and the activation of CD8+ T cells by the A2 phenotype is not ineffective in this case. In patients with the CW2 phenotype, we see a relative suppression of humoral immunity. Compared to healthy individuals, in addition to a significant reduction in immunoglobulin (Ig)M, there was a 1.9-fold reduction in CD20+ lymphocytes. In the presence of CW2, macrophage activation increases 1.4 times compared to the control group, but it is not used to eradicate parasites but rather to concentrate and replace parasites. There is a negative correlation between CW2 and CW4 that work to reduce CD16+ cells [8,54].

The following are some key factors awaiting response:
• Behavioral pattern and life cycle of human Demodex mites (II) The relationship between the increasing prevalence of Demodex with increasing age (III) pathogenesis, and interaction between Demodex Folliculorum and Demodex Brevis throughout the body; (IV) virulence factors (V): Relationship between parasite density and disease clinical signs [19].

There is little information available on the treatment of Demodicosis and the main reasons include the following:
• There are no ideal systems in vitro or ex vivo to test the efficacy of drugs and test their minimum inhibitory concentration. (II) Clinical diagnostic confusion of primary Demodicosis infection and inflammatory disease (III) The dual effects of anti-inflammatory and antimicrobial drugs on many factors.

The effects of Ivermectin have been proven as an acaricidal and is used in the treatment of Demodex in humans and dogs [55-57]. The dose of oral ivermectin for the treatment of canine Demodicosis is higher than in humans. Although topical use of other Acaricides, such as Permethrin 5%, Benzyl benzoate 10-25%, Crotamitone 10%, Lindane 1%, or Malathion 5% has been confirmed for the treatment of scabies, current evidence for their effectiveness in the treatment of Demodicosis is very limited. The ability of topical Benzyl benzoate 10 % has been demonstrated in only a small number of patients to eradicate Demodex parasites [58-60].

3.4. Relationship Between Demodicosis and Diseases

The results show that Demodicosis plays a role in the development of dermatitis around the mouth, oral postulates, and even blepharitis due to mental problems and stress [12]. In Chang's study on people with rosella, a significant relationship was found between the Demodex parasite and rosacea [61]. In another study, the results showed that Demodex parasites were more common in people with blepharitis than in non-patients [62].

Harmlin et al. noted that there is a link between heart disease and the prevalence of Demodex parasites due to the stimulation of the immune system by Demodex and the development of an immune response to heart valve cells [63]. According to the results, all adults have a percentage of Demodex infection, and as this density increases with this parasite, skin and hair lesions increase and are directly related, so Demodex treatment can reduce skin issues [64,65].

3.5. Role of Demodicosis in the Pathogenesis of Rosacea

Rosacea is a common dermatosis of the face, which has a prevalence of up to 10% considering all its forms [66]. Rosacea is one of the most common skin diseases that has a chronic inflammatory nature and is characterized by inflammation, papules, telangiectasia, edema, pustules, or a combination of these symptoms [67,68]. While various factors have been suggested for the possible causes of this disease, the exact etiology of rosacea is still unknown [69].

An abnormal increase in Demodex with an increased risk of rosacea has already been seen. Flow cytometry analysis has shown that the influx of Demodex and rosacea can affect blood as well as skin homing T cell subset levels triggered against each other. This trend is assumed by microorganisms carried by mites and/or exposure to exoskeleton components, and it occurs as a result of rosacea-associated inflammation [49].

The proliferation of the Demodex mite in patients with rosacea is, in most authors' beliefs, a secondary event, an epiphenomenon, or an aggravating factor in which the initial inflammation plays a role in promoting the proliferation of Demodex, which then exacerbates the disease [66]. Rosacea has been proven to be an effective factor in Demodex infection in eyelashes, and it is independent of age and sex and has a higher prevalence in papulopustular types. Suspicion of Demodex infection in patients with Rosacea is acceptable. Similarly, treatment of Demodex in rosacea may reduce their clinical manifestations even if the rosacea is not ocular. Further detection of Demodex in the hair follicles of patients with rosacea can lead to better diagnosis and possibly modification of the disease process [70].

According to the results, Demodex mites complicate the clinical picture and the process of rosacea. Analysis of the clinical picture and the course of the disease in patients with rosacea associated with Demodex mites revealed that the parasite develops acute inflammatory morphological elements and increases the duration of the rosacea disease [71].

4. Differences and Similarities Between Canine and Human Immune Response

4.1. Innate Immune Response

Live Demodex parasites, derived from the natural skin of the face, modulate the immune system by acting on human immortal sebaceous gland cells, which act through secretory active molecules to express TLR2 [72]. A wide range of cell types expresses pathogen recognition receptors against the infiltrating pathogens, which play an important role in the host innate immune system. Testro et al. showed that mammalian TLRs provide innate immunity with marked specificity against a large number of microbial pathogens. The signaling pathways of TLRs regulate gene expression of cytokines, co-stimulatory, and adhesion molecule production [6].

In human Demodicosis, factors such as carbohydrate-like Tn antigen (expressed by Demodex) and secretion of pro-inflammatory mediators like IL-8 and tumor necrosis factor (TNF)-α from the pilosebaceous unit may play a role in the innate immune response of the host to facilitate the invasion and population expansion of Demodex. Additionally, mites' infestation can elevate tear cytokine levels, especially IL-1β and IL-17, which can cause inflammation of the lid margin and ocular surface in some individuals [3]. The studies did not find a significant difference between the amount of TNF- α produced by infected cells and treated cells and also did not show a significant change in phagocytic activity and index, but a decrease in the functional activity of leukocytosis was observed in primary Demodicosis in humans [7].

Similarly, the expression level of TLRs in dogs with Demodex has also been suggested as an important factor, and significantly increased TLR2 expression and decreased TLR4 and TLR6 expression has been observed in peripheral blood samples isolated from infected dogs compared to control animals [73]. Induction and progression of primary canine Demodicosis, including anti-inflammatory pathways associated with increased cholinesterase activity, and in addition, cytokine IL-10, which has both anti-inflammatory and immunosuppressive activity, is associated with the development of recurring canine Demodicosis [27].

4.2. Adaptive Immune Response

From the results of the first research, the role of immune response T cells can be mentioned [27]. Helper T cells known as the adaptive immune response, can infiltrate the site with other immune response cells, including macrophages and Langerhans cells [3]. In the lesions caused by Demodex-related rosacea, concentrations of helper T cells have been observed. In consolidating the importance of helper T cells, we can mention the inflammatory infiltration in the follicles in rosacea patients with Demodex infection, which has a higher level compared to macrophages and Langerhans cells. so they are known as type IV immune reactions [74]. It has been shown that in individuals with primary Demodicosis, a significant decrease in the level of lymphocytes and T cell subsets is observed in the collected peripheral blood samples [75]. Flow cytometry analysis of blood samples collected from individuals with human Demodicosis and healthy individuals showed that in the patient group, there were more T9 and T reg cells in the blood samples

and in skin homing T cell populations compared to the control group. Also, in confirmation of this claim, sebocytes, after facing the Demodex challenge, increased the release of cytokine IL-10 with the help of T regs [49,72].

Haeley et al. demonstrated the role of cellular immunity in canine Demodicosis. Other studies of canine Demodicosis have reported that although CD4+ and CD8+ lymphocyte populations are equal in the perifollicular dermis, cells in the furunculosis lesions and infiltrated follicular epithelium are composed mostly of CD3+ and CD8+ T cells [27, 76]. Dog Demodex parasites have been reported to escape adaptive immune attack by inducing lymphocyte apoptosis [77].

The importance of the humoral immune response during primary Demodicosis has not yet been determined because no significant differences in circulatory immune complex, serum complement activity, phagocytic activity, and serum antibody (IgA, IgG and IgM) levels were observed between healthy individuals and the Demodicosis group. While blood IgM levels in patients were significantly higher than the control group [7,75].

In studies performed with skin sampling of dogs with Demodicosis, the presence of IgG-bearing plasma cells was at a higher level than IgA-and IgM-bearing plasma cells, while in follicular epithelium and peri-follicular dermis, IgG positive plasma was evident in such a way that the presence of IgG4 in per-folliculitis lesions and IgG2 or IgG4 in folliculitis or furunculosis samples were largely positive [27].

In another study, Pit Bull Terrier dogs with primary Demodicosis, no difference in serum IgM, IgG, and IgE levels were observed between controls and patients, but higher serum IgA was reported in patients [78]. High IgG secreting plasma cells were found in canine skin samples with Demodicosis, Although the exact role of the humoral response against human Demodicosis is not entirely clear. Therefore, it seems that the adaptive immune system against Demodicosis may consist of both humoral and cellular responses [79].

5. Conclusion

It seems that the host immune system appears to recognize and tolerate the presence of these mites, although the physiological role of human Demodex mites in healthy skin remains unclear, especially the way in which they escape the innate immune system is very important. The clinical distinction between Demodicosis and inflammatory dermatoses, such as papulopustular rosacea or dermatitis around the mouth, should be considered. Despite the close genetic relationship between Demodex Folliculorum and Demodex Brevis they show different clinical and cellular manifestations in humans and dogs. Advances in the availability of appropriate in vitro or in vivo models for future experimental studies could be a major step forward in immunological studies and a full understanding of the pathogenesis of the disease, as well as how they reproduce in the host, which leads to the further development of new treatment strategies.

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