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Review Article

The immunology of susceptibility and resistance to scabies

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SUMMARY

The transmission of scabies occurs with the burrowing of Sarcoptes scabiei var. hominis mites into the skin. Infestation invariably leads to the development of localized cutaneous inflammation, pruritis and skin lesions. Classical transmission studies document an initial increase in S. scabiei numbers subsequent to primary infestation with a gradual reduction as host immunity develops. However, certain individuals fail to control infection and develop severe crusting of the skin, accompanied with extremely high mite burdens, elevated antibody levels and eosinophilia. These individuals have the nonhealing form of the human disease known as crusted scabies. The genetic predisposition for susceptibility or resistance to S. scabiei infection in humans is hypothesized to correlate with the dominance of an IgE-driven Th2 response in severe disease or an interferon-γ-dominated Th1 response that promotes parasite control. However, recent data reveals complexities in cytokine regulation in the skin and the mechanisms of acquired resistance and immune escape. In this review, we consider the recent immunological and biomolecular advances in understanding the human host immune response to S. scabiei infestations in the context of earlier studies and attempt to reconcile apparent differences and emphasize those aspects of the Th1/Th2 model that are supported or refined.

Keywords *host immunity, immune markers, inflammatory skin disease, parasitic skin diseases, Sarcoptes scabiei, scabies*

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INTRODUCTION

Human responses to parasitic infections have often been difficult to define as either Th1 or Th2, as characteristics from both response types are often reported (1). However, there is accumulating evidence that the host immune response to crusted scabies resembles a nonprotective Th2 allergic response, and ordinary scabies resembles a Th1 cell-mediated protective response (2–5). Th1-biased immune reactions are dominated by $CD4^+$ and $CD8^+$ T cells secreting IFN-γ and IL-2 (6). Th2-biased T cells (secreting net IL-4, IL-5 and IL-13) are dominant effector cells in the pathogenesis of IgE-mediated hypersensitivity including attracting, activating and prolonging the survival of nonspecific effector cells. The Th1/Th2 concept has also been extended to T-regulatory populations expressing IL-10 and transforming growth factor-β (TGF-β). Eosinophils, basophils and mast cells are major effector cells in the pathogenesis of allergic diseases, and it is thought that their cytoplasmic granule-associated or lipid mediators contribute to many of the signs and symptoms that are characteristic of these diseases as well as contributing to protective host responses, especially to parasites. IL-17 is another major subset of $CD4^+$ T cells that have been linked to host immune responses to extracellular bacteria and fungi. IL-17 is recognized as stimulating many cells of the innate immune system particularly recruiting and activating neutrophils to sites of inflammation as well as stimulating endothelial and epithelial cells to synthesize inflammatory cytokines IL-1, IL-6 and TNF-α (7). However, the host immune defence against infectious diseases has many multiple overlapping systems for avoidance of immunopathology, and pathogens have evolved many interference mechanisms for immune evasion and survival. It may therefore be more appropriate to define combinations of cytokines and effector cells at particular stages of the response when describing the immunopathology of scabies and attempts by the host immune response to clear the mite.

Clinical features

Ordinary scabies

Presentation with a primary infestation of scabies usually occurs 4–6 weeks after infection and is characterized by a generalized itching often more intense at night. The pruritic papules in human scabies are typically restricted to the webs of the fingers, followed by wrists, elbows, periumbilical skin, buttocks, ankles, the penis in men and the periareolar region in women. Total mite numbers in humans are usually self limiting, in the region of 10–12 mites per patient (8). Spontaneous recovery of scabies in humans has been described to only occur with subsequent reinfestations. Immunological memory to mite antigens has been demonstrated with an induction time of only 24 h for hypersensitivity with patients infested for a second time (8). Additionally, parasite numbers were significantly reduced, and in approximately 60% of the cases reinfestation of sensitized hosts was unsuccessful. The clinical appearance of scabies can be wide ranging, but the classical clinical sign for diagnosis is the burrow, found in the horny layer of the epidermis. Diagnosis can be problematic, (9) and in some situations the rash and itch of scabies can persist for up to several weeks after curative treatment, possibly attributed to dead mites or mite products remaining within the skin layers. In chronic infestations, atypical excoriation and eczematization of the skin may develop. Patients taking topical or oral steroids or who are immunosuppressed because of other disease also present uncharacteristically. In some cases, nodular scabies can develop, which can persist for several months after successful treatment. These firm red-brown nodules are often extremely itchy and are commonly found in the groin, buttocks and periumbilical area.

Crusted scabies

Historically known as Norwegian scabies, this debilitating disease is characterized by large numbers of mites, high total IgE and IgG levels, peripheral eosinophilia and the development of hyper-keratotic skin crusts that may be loose, scaly and flaky or thick and adherent (10). The distribution over the body can be localized or extensive and include the neck, scalp, face, eyelids and under the nails. Crusts reveal large numbers of mites and eggs, totalling over a million in the most severe cases (11). Crusted scabies is caused by the same species of mite that causes ordinary scabies with no evidence that mites in patients with severe disease differ in virulence to mites in ordinary scabies. Progression from ordinary scabies to crusted scabies is uncommon, and susceptibility to severe disease has been related to a range of predisposing conditions. These include leprosy, infection with HTLV-1 and HIV and those immunosuppressed by medication. However, crusted scabies has been observed in overtly immunocompetent individuals, and some cases familial clustering has been detected, suggesting the possibility of a specific immune defect (12). As crusted scabies has been linked historically with leprosy patients, this also suggests a common genetic predisposition and the hypothesis that the immune defect predisposing to clinical disease in leprosy may also predispose to hyperinfestation following *S. scabiei* infestation (2). However, causal genetic factors are currently unknown and are not the subject of this review. Crusted scabies can also occasionally occur locally in a paralysed limb or a limb with sensory neuropathy, presumably reflecting lack of itch or inability to scratch (13). Crusted scabies has also been observed in patients with cognitive deficiency and in institutionalized patients seemingly because they are unable to properly interpret the associated pruritis or are unable to physically respond to the itching (14). Fissuring and secondary bacterial infections are common and are associated with the high mortality rates(15).

HUMORAL IMMUNE RESPONSE TO *S. SCABIEI*

It is clear from multiple studies that infestation with *S. scabiei* var. *hominis* provokes an increase in circulating antibodies; however investigations into humoral immunity in scabies patients have shown contradictory results.

IgG and IgM

A number of studies have documented that total IgM and IgG levels were significantly higher in ordinary scabies patients than in controls both before and after treatment of the disease (16–20). Conversely, other studies showed no significant differences in IgM and IgG immunoglobulin levels between patients with scabies and the control group (21,22), whereas another study observed a decrease in total IgG and IgM post-treatment (23). It is therefore uncertain whether these antibody levels are specific or related to associated secondary bacterial infections, as serum immunoglobulin levels in one study did not correlate with the density of mite or the duration or intensity of infestation (18). In contrast, a retrospective study of 78 cases of crusted scabies in Australia showed 56/58 of patients had elevated total IgG, with the median level recorded over double normal rates (3). This is supported by a more recent study documenting elevated levels of total IgG, IgG1, IgG3 and IgG4 in sera from patients with crusted scabies (4). Notably, recent unpublished studies investigating scabies-specific antibody levels in patients with both crusted scabies and ordinary scabies using multiple

S. scabiei var *hominis* recombinant antigens showed no significant differences in binding levels of scabies- specific IgG, IgG1 and IgM between scabietic and control groups (Walton S.F., unpublished data).

Binding of IgG and IgM antibodies to a pathogen activates the complement cascade which augments the activities of these antibodies. Serum levels of C3 and C4 in scabies infestations have been investigated with no change observed preceding, during or post-treatment, or between patient and control groups (18,24–27). Surprisingly, levels of C3 and C4 were recorded as decreased in the sera of patients with crusted scabies which, given the large inflammatory responses related to this condition, would normally be expected to have hyper-complementaemia (3). However, C3 has been documented in dermal blood vessels of crusted and ordinary scabies, and fibrinogen observed in dermal tissue (4,25). These features suggest an activated complement system generating potent inflammation, although the specificity of this activation is unknown and could relate to secondary bacterial infection.

IgA

A significant decrease in total IgA values has been observed in patients with ordinary scabies compared to the controls (16,18,22,23,25). However, in another study no significant differences were reported, (20) and in the case series of patients with crusted scabies IgA levels were documented as elevated in 64% of patients (3). Secretory IgA is important in local (mucosal) immunity and is the predominant antibody in external secretions such as sweat, saliva and tears, as well as in intestinal and respiratory secretions, after stimulation. IgA does not activate complement and opsonizes only weakly. Interestingly, scabies-specific IgA binding levels to a scabies mite recombinant protease were significantly increased in both ordinary scabies and crusted scabies patient groups compared to control subjects (Walton S.F., unpublished data). Immunohistochemistry results demonstrate *S. scabiei* proteases localizing in the mite gut and scybala, suggesting they are involved in mite digestion and skin burrowing. Therefore, it is possible that the increased secretions of proteases into the skin by scabies mites may in part induce the increased levels of *S. scabiei*-specific IgA observed in the blood.

IgE

There is increasing evidence that IgE is important in the host defence against scabies mites, as in the host immune response to a variety of other parasites. However, once again while total IgE levels have been observed to be elevated by a number of researchers in ordinary scabies (4,18,22,24,27–30) and decreased after treatment (23,31,32), others investigations report no differences (16,19). This disparity could be attributed to lack of sensitivity with the assays or related to the timing of blood collection, disease progression or other unknown factors causing an immune response in the host. However, as for IgG levels, measurement of total serum IgE appears to be of no benefit in the preliminary clinical investigation into a suspected host.

Conversely, dramatic increases in total IgE levels have been documented for crusted scabies (4,27,33,34). Roberts *et al.* (3) document 96% of 52 cases with elevated IgE, with 73% 10× above normal levels, and 10% 100× above normal levels. Immunoblotting studies demonstrated that sera from patients with crusted scabies showed strong IgE binding to 21 unidentified *S. scabiei* var. *canis* proteins in comparison with ordinary scabies in which only six proteins were weakly recognized (35). Studies using *S. scabiei* var. *canis* whole mite extract to measure scabies-specific IgE binding observed elevated levels in approximately 50% of patients with active ordinary scabies (36). Recent serology results using *S. scabiei* var *hominis* recombinant proteins indicate patients with both crusted scabies and ordinary scabies have a defined IgE and IgG4 response to a number of scabies mite recombinant antigens (Walton S.F., unpublished data). Significantly greater IgE binding to a number of these proteins was observed in the sera of patients with crusted scabies compared with ordinary scabies and control groups, and similarly significantly increased IgE binding of the sera of patient with ordinary scabies was observed compared with control sera.

Immunohistochemistry staining of mite-infested skin biopsies from patients with crusted scabies has shown human IgG and IgE localizing in the mite gut and flooding the mite burrow (37) (Walton S.F., unpublished data). In addition, polyclonal antibody to multiple *S. scabiei* var. *hominis* recombinant proteins has been demonstrated binding to the gut, external cuticle and burrow of the scabies mite (9,38) (Walton S.F., unpublished data).

Immediate wheal reactions have been elicited by intradermal injection of scabies mite extracts in patients with both ordinary scabies and crusted scabies but not normal volunteers (39,40). This response was observed to wane with time, and patients injected 15–24 months after infestation did not react. IgE antibody to allergens induces early allergen-specific mast cell degranulation and contributes to the late-phase reactions by chronic tissue damage via the downstream effect of mast cell mediators and by facilitating allergen presentation to T cells. Mast cell activation also leads to the recruitment and activation of basophils and eosinophils, both of which express the Fc

receptor on their surface and can therefore contribute to the IgE-mediated immune response. Eosinophilia has been reported a number of times in crusted scabies (3,41,42), whereas expression of eosinophilia in patients with ordinary scabies varied between studies, and often eosinophils were only observed in skin lesions containing a mite (26,43).

Animal studies

Animal studies show a clear increase in circulating antibody in the mite-infested host and a rapid response to re-infestation, accompanied by a spontaneous clearance or significant reduction in mite numbers. Arlian *et al.* (44) demonstrated that IgG antibodies to *S. scabiei* var. *canis* whole mite extract in four different infested host species and *S. scabiei* var. *canis*-infested rabbits and dogs had elevated serum levels of total immunoglobulin, IgE and IgG compared to controls (36,44–46). Studies in sheep demonstrated that primary infestations with either *S. scabiei* var. *ovis* or *Psoroptes ovis* elicited significant increases in levels of IgG, IgE and IgM that were reduced with challenge infestations (47,48). Vaccination of goats with separated mite proteins invoked high levels of scabies-specific IgG but failed to induce specific IgE. In contrast, goats challenged experimentally with a primary or repeated mite challenge developed strong serum IgE and IgG antibody responses to *Sarcoptes* antigens (49). Antibody IgG responses to whole mite *S. scabiei* antigen in pigs have also been widely described using commercial ELISA tests with varying sensitivity and specificity (50–52). However, more recent results suggest that a diagnosis of sarcoptic mange in pigs may not correlate with serum IgG against crude extract of *S. scabiei* (53).

In summary, it appears that patients with crusted scabies have significantly elevated total and *S. scabiei* specific IgE levels in comparison with patients with ordinary scabies, in which weaker and more varied responses are documented. It seems the pronounced humoral response in crusted scabies is comparable to that observed for animal infestations, but in the case of crusted scabies the immune response is unprotective and unable to control or reduce the mite burden even when challenged in sequential infestations.

SKIN IMMUNE RESPONSE TO *S. SCABIEI*

Human skin harbours a variety of immune response-associated components that together form the skin immune system, which consists typically of lymphocytes, Langerhans cells, dermal dendritic cells, keratinocytes, granulocytes and skin-draining regional lymph nodes. Regulation of the skin defence mechanism is important as abnormal or inappropriate immune reactions lead to pathogenesis of skin disorders including dermatitis, psoriasis and eczema. Exposure to antigens/allergens can lead to allergic skin disorders such as atopic dermatitis, urticaria and allergic contact dermatitis. T cells play a central role in the activation and regulation of immune responses by recognizing antigen and inducing cytokine production. Furthermore, keratinocytes are known to produce pro-inflammatory cytokines IL-1, IL-6, IL-8 and TNF-α, and the immunomodulatory cytokines IL-10 and IL-12, originating from keratinocytes, are considered to be responsible for systemic effects (54).

A number of recent studies support the proposition that scabies mite proteins play a complex role in the host skin immune response via modulation of cytokine and chemokine secretions and expression of adhesion molecules from resident skin cells such as fibroblasts, keratinocytes and endothelial cells. Recent *in vitro* studies document IL-1α and IL-1β secretions upregulated in the cell culture supernatant of human skin equivalents when stimulated with *S. scabiei* var. *canis* whole mites (55). Subsequent studies by the same group show unknown components in whole mite extracts of *S. scabiei* var. *canis* downregulate secretion of interleukin-1 receptor antagonist (IL-1ra) and IL-8 and stimulate secretion of IL-6 and vascular endothelial cell growth factor (VEGF) in cultured normal epidermal keratinocytes (56). In the same study IL-6, IL-8, granulocyte-colony stimulating factor (G-CSF) and VEGF were upregulated in cultured normal human dermal fibroblasts. Of interest, when keratinocytes were cultured in the presence of inflammatory cytokines (IL-1α and IL-1β, TNF-α and IL-17), the same *S. scabiei* var. *canis* extract was shown to still downregulate levels of IL-8 secretion and also granulocyte/macrophage-colony stimulating factor secretion from cultured fibroblasts (57). Furthermore, in this latter study levels of the growth-related oncogene alpha (GROalpha), TGF-α and cutaneous T-cell attracting chemokine from keratinocytes and IL-6 and G-CSF from fibroblasts were also downregulated. Another study using stimulated cultured dermal microvascular endothelial cells documents that the var. *canis* extract inhibits the expression of intracellular adhesion molecule-1 and E-selectin and downregulates secretion of IL-1α (58). Furthermore, these observed inhibitory effects were not altered in the presence of histamine and lipid-derived biologic mediators (59). Over all, these findings confirm uncharacterized mite proteins have immunomodulatory properties that favour invasion of the host by the parasite via down regulating or depressing inflammatory processes of resident cells in the skin and possibly influencing a delayed immune reaction. Interestingly, recent reports describe the proteolytic

activity of house dust mite (HDM) cysteine and serine proteases stimulating human keratinocytes and upregulating IL-8 secretion *in vitro* (60,61). The specific effects of scabies mite cysteine and serine proteases, homologues of the HDM cysteine protease group 1 and 3 allergens, on keratinocytes still remain to be elucidated (62–64). Similarly, the effect on the skin immune system of other reported scabies mite homologues to HDM allergens is also currently unknown. These include a scabies mite mu class and a delta class glutathione *S*-transferase group 8 allergen implicated as a major allergen in crusted scabies immune response (65,66), localized to the mite gut (9); and an apolipoprotein, homologous to the C terminus of group 14 allergen (67).

Cellular immune response

To date, cell-mediated host immune responses have been primarily identified by histopathological examination of skin biopsies from scabietic lesions. The severe itching and papular rash of a primary ordinary scabies infestation have skin lesions characterized by inflammatory cell infiltrates typical of a delayed sensitivity cell-mediated immune reaction. Histopathological examination of skin biopsies from scabietic lesions reveals mite burrows surrounded by inflammatory cell infiltrates comprising eosinophils, lymphocytes and macrophages. Predominantly, $CD4^+$ T cells are observed to dominate the lymphocytic infiltrate of inflammatory skin lesions in ordinary scabies, with a reported CD4/CD8 ratio of 4 : 1 (68). However, biopsy specimens containing both mites and inflammatory papules were observed to also contain IgE deposits in vessel walls in the upper dermis, suggesting the occurrence of Type 1 hypersensitivity reactions in some cases (68).

In contrast, immunohistology studies on patients with crusted scabies suggest the inflammatory skin response is comprised of predominantly $CD8^+$ T cells (4). Microscopy showed the strong presence of T cells (anti-$CD45^+$, anti $CD43^+$), but interestingly no evidence of any B cells (CD20), and only the occasional macrophage was evident. A predomination of infiltrating CD8 T lymphocytes in the dermis was observed. The proportions of T and B lymphocytes and T-cell subsets in the blood of these patients were within normal ranges, indicating a selective movement of CD8 T cells into the dermis. Activated $CD8^+$ T cells in crusted scabies lesions may induce dysregulated keratinocyte apoptosis contributing to the elicitation and progress of epidermal hyperproliferation. This is comparative with psoriasis in which a pronounced $CD8^+$ epidermotropism into the epidermis and dermis has been observed (69). These results suggest skin-homing cytotoxic T cells contribute to an imbalanced inflammatory response in the dermis of crusted scabies lesional skin and may add to the failure of the skin immune system to mount an effective response resulting in uncontrolled growth of the parasite. Strong staining for the inflammatory cytokine IL-1β and anti-inflammatory cytokine TGF-β was also observed in crusted scabies skin lesions. The observation of the anti-inflammatory cytokine TGFβ suggests some immune regulation occurring in CS lesional skin as TGFβ is a known immunosuppressive cytokine produced by monocytes and T cells that inhibits cell growth and induces IgA secretion (70).

The clinical picture of psoriasis is somewhat similar to crusted scabies and is characterized with erythematous scaly papules and plaque formation as a result of abnormal keratinocyte hyperproliferation and infiltration of inflammatory cells into the epidermis and dermis. Data suggests psoriasis is induced and maintained by a complex pattern of overexpressed Th1 cytokines such as IL-2, IL-6, IL-8, or IFN-γ and TNF-α (71). Preliminary studies on cytokine production obtained from fresh peripheral blood mononuclear cell (PBMC) collected from patients with crusted scabies and uninfested controls in northern Australia demonstrated a statistically significant elevation of IL-4 in crusted scabies (10). It has been shown that IL-4 can stimulate keratinocyte proliferation (72), that epidermal cells have IL-4 receptors, and IL-4R expression is elevated in psoriasis (73). Microarray analysis of two PBMC samples obtained from a recurrent crusted scabies patient (one obtained when the patient had severe disease and the other after treatment and apparent cure) revealed significant upregulation of amphiregulin and epiregulin at the time of severe disease (Walton S.F. and Currie B.J., unpublished data). Both proteins are members of the epidermal growth factor family and are associated with growth of normal epithelial cells. Over expression has also been associated with a psoriasis-like skin phenotype (74,75).

Recent results have identified patients with both crusted scabies and ordinary scabies to have strong PBMC proliferative responses to multiple *S. scabiei* homologues to HDM allergens (Walton S.F., unpublished data). Studies show for the first time that clinical phenotype, i.e. ordinary vs. crusted scabies, is associated with differences in the type and magnitude of the immune response to *S. scabiei* proteins. Quantitative analysis of cytokine levels showed the IFN-γ/IL-4 ratio was significantly higher in supernatant from *S. scabiei* stimulated PBMC from patients with ordinary scabies compared to patients with crusted scabies, and increased levels of IL-5 and IL-13 were observed in stimulated PBMC from crusted scabies compared to patients with ordinary scabies. These latter results support the hypothesis of nonprotective Th2 activity in patients with crusted scabies, leading in part to the documented

high levels of total and specific IgE observed and the growth and development of mast cells. This has been detected in similar studies of HDM allergy, particularly with the immunodominant allergens *Der p* 1 and *Der f* 1 (76). Additionally, scabies mites have been reported to secrete unknown antigens that stimulate the proliferation of T-regulatory cells and their secretion of IL-10, which would inhibit the inflammatory and immune responses in humans to the mites (77).

Innate immune response to *S. scabiei*

Tissue and blood feeding parasites face significant threats to their early survival caused by host innate immune responses. Scabies mites feed on epidermal protein and host plasma and thus are also exposed to host defence mechanisms both internally and externally. Complement has been shown to be an important component in host defence against blood feeding ticks, as for many other pathogens (78,79). Serine proteases from the cattle parasite *Hypoderma lineatum* and laval secretory/excretory products (predominantly chymotrypsin) from the sheep blowfly *Lucilia cuprina* are able to deplete activity of both alternative and classical complement pathways of the host via C3 degradation (80,81). Recent molecular data describes a family of multiple scabies mite homologues of the group 3 serine protease allergens (63,82). The 33 sequences identified cluster into three major clades with all but one containing mutations in the catalytic triad ruling out the possibility that they can act as proteases by any known mechanism. Two recombinantly expressed scabies mite-inactivated protease paralogues (SMIPPs) were demonstrated as inhibiting all three pathways of the human complement system (83). Both SMIPPs exerted their inhibitory action because of binding of three molecules involved in the three different mechanisms which initiate complement: C1q, mannose binding lectin, and properdin. Both SMIPPs bound to the stalk domains of C1q, possibly displacing or inhibiting C1r/C1s, which are associated with the same domain. The x-ray crystal structures of the two SMIPPs have been determined, (84) but no common structural mode of complement inhibition was apparent. The *in vivo* effects of these molecules are still unknown, although the decreased levels of C3 and C4 observed in patients with crusted scabies are interesting given the large inflammatory nature of this condition and could possibly relate to higher levels of SMIPPs expressed by the presence of millions of mites in the skin.

Granulocytes are innate effector cells in the host immune defence against many multicellular parasites. Recent emerging data now highlights granulocytes with immunomodulatory roles as well, able to produce cytokines and chemokines that can bias the immune response in a particular direction (85). Eosinophils, mast cells and basophils are reported as responsible for the initiation and ongoing regulation of Th2 responses. They can be rapidly recruited to sites of infection and draining lymph nodes where they produce IL-4 and/or IL-13 (85). Skin biopsy sections from crusted scabies lesions showed large numbers of infiltrating lymphocytes and eosinophils in the dermis, in conjunction with blood eosinophilia and enhanced production of IgE (4). However, there have been no investigations reported to date on the role and importance of granulocytes in the Th2 biased immune response of crusted scabies.

Future vaccine and immunotherapy development

Emerging resistance by scabies mites to currently available chemotherapeutics permethrin and ivermectin highlights the need to identify potential targets for chemotherapeutic and/or immunological intervention (10,86–88). Parasite modulation and evasion of host immunity facilitates survival in host tissues and is a critical factor in pathogenicity and transmission. There is much to be gained in understanding the vast and complex array of immunological interactions occurring between parasite and host. Currently, no reliable histological or genetic test is available to determine whether a patient will develop crusted scabies, and hence a definitive diagnosis can often only be determined once a patient has severe disease. An understanding of genetic and immunological changes occurring in crusted scabies may aid discovery of potential targets for therapy, as well as allowing the early discrimination of ordinary from the severe form of the disease. Patients with crusted scabies typically respond poorly to conventional topical chemotherapy such as 5% permethrin, therefore immunotherapy similar to that currently used for allergic skin disorders, such as the administration of allergen extracts, may offer a better alternative (89). Allergen immunotherapy is indicated for patients with demonstrated specific IgE antibodies against clinically relevant allergens (90). Allergen immunotherapy involves the administration of gradually increasing quantities of specific allergens to patients until a dose is reached that is effective in reducing the severity of disease from natural exposure. The aims are to redirect an inappropriate immune response against allergens or autoantigens with the help of a range of suppressor mechanisms, and include reducing the inflammatory response and preventing development of persistent disease in the long term. An alternate method is to produce modified hypoallergenic derivatives of recombinant allergens with reduced likelihood of adverse effects. Another promising

approach incorporates immunotherapy with T-cell peptide epitopes. Short allergen-derived synthetic peptides can induce T-cell anergy and have been shown to inhibit T-cell function and are unable to cross-link IgE to cause anaphylaxis. Vaccines designed to directly target the scabies mite are also a possibility especially in the light of the partial success of a vaccine for the cattle tick *Boophilus microplus (*91,92) and approaches to a vaccine for *P. ovis* (93,94) Development of vaccines, immunotherapeutics and immunodiagnostics represents a promising long-term strategy to control scabies in endemic Indigenous communities in northern Australia and other affected communities elsewhere in the world. However, a comprehensive understanding of the localized immune response in the skin is critical to target the response away from pathology to immunity. Newly developed vaccines for other diseases on occasion have been shown to cause detrimental effects, especially in diseases where the basic biological processes are unresolved (e.g. early rheumatic fever vaccine). DNA vaccines consist of plasmid vectors with genes that encode allergens. DNA vaccines express antigens *in vivo* and thus can access the MHC-I pathway for presenting antigen to antigen presenting cells and induce Th1 type immune response (95). This vaccine approach in animal models has been shown to significantly decrease Th2-mediated responses, enhance Th1-mediated responses, and suppress the allergic response (96). Although still in the early stages of development, with a number of challenges to overcome, this concept has potential to be applied to the development of safe and specific DNA vaccines for prophylaxis and therapy of crusted scabies.

CONCLUSION

Understanding the immunology of scabies is still in its infancy. Continuing support for molecular and immunological discoveries in scabies research will aid in the identification of the mechanisms of protection operating in resistant naturally acquired immunity and comparing these with the enhanced Th2 allergic mechanisms operating in severe disease. The mining of *S. scabiei* EST databases for sequences encoding proteins with homology to known immunological targets in other similar species or those performing functions critical to survival is currently being explored. Downstream studies using recombinant proteins are likely to provide significant information in characterizing the host immune response and determining preventative or immunotherapeutic approaches to disease control. Investigating innate and antibody-dependent and independent immune activation in scabies will also help highlight the structural and functional mechanisms of immune evasion and survival by the parasite and potential drug targets for chemotherapeutic interventions.

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