Novel insights into an old disease: recent developments in scabies mite biology

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Purpose of review
Scabies is a serious disease of both humans and other animals caused by infestation of the skin with the ectoparasitic mite *Sarcoptes scabiei*. Our current understanding of scabies mite biology and disease processes is far outweighed by the significant, worldwide impact of the disease. This review summarizes the recent data which furthers our knowledge of mite biology, host specificity and parasite host evasion mechanisms.

Recent findings
Recent data concords with the previous work demonstrating limited gene flow between different host-associated populations of scabies mites. This evidence of the host specificity of scabies mites has important implications for disease control programmes. Other studies have begun to decipher the molecular basis of the complex host–parasite interactions underlying scabies infestations. Scabies mites have developed complex mechanisms to interfere with the host defence processes that may also enhance the survival of the associated skin microbiome, consistent with the epidemiological evidence. Recently developed natural host models of scabies are valuable tools to further study the disease processes and to trial novel therapeutic agents.

Summary
Although significant progress has been made, further research is needed to understand the biology, host–parasite interactions and pathogenesis of this ubiquitous parasite.

Keywords
complement, genome, host defence evasion, host specificity, *Sarcoptes scabiei*

INTRODUCTION

The serious impact of scabies, caused by infestation of the skin with the ectoparasitic mite *Sarcoptes scabiei*, is well established. Scabies has been estimated to affect around 300 million people at any one time [1], largely in disadvantaged communities. It is also a widespread veterinary problem, with infestations recorded in over 100 species of mammals [2]. Despite the significance of this disease, our understanding of mite biology and host–parasite interactions has been limited.

The obligate parasitic lifestyle of *S. scabiei* precludes successful in-vitro culture. Consequently, experimental studies have been extremely challenging. A model of dog scabies mites infesting New Zealand white rabbits [3] provided the opportunity to study the biology of scabies mite infestations. Many years later, opportunistic mite sampling from natural infestations in humans and foxes enabled the generation and analysis of cDNA libraries which yielded the first large-scale genetic analysis of scabies mites [4–6]. Here, we will review the recent advances in the understanding of scabies mite biology, host-specificity and host–parasite interactions, many of which were facilitated by and built on these early advances.

IN-VIVO MODELS OF HOST INFESTATION

Most studies investigating the host response to scabies focus on the acute phase of disease during natural infestation. This is true of the recent studies of the systemic host response to scabies that assessed the measures of oxidative stress in dogs [7], goats [8] and camels [9], haematology and serum

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KEY POINTS

- The development of in-vivo models of infestation will facilitate important advances in the understanding of host–parasite interactions and disease.
- Scabies mites are ubiquitous, affecting a multitude of mammalian species; however, there is evidence of host specificity and limited gene flow between host-associated mite populations.
- Scabies mite complement inhibitors are likely just one branch of a yet largely unexplored machinery of host evasion mechanisms that may be possible targets for protective intervention.
- Scabies mite infestation should be viewed as a complex disease likely involving a change in the status of the skin microbiome, which gives rise to serious secondary infections.
- Comparative genomics of related astigmatid mite pests will likely provide a foundation of information that will be of enormous value for future research on the disease they cause.

biochemistry in free ranging racoon dogs [10] and acute-phase protein responses in the capybara [11] and the Alpine ibex [12].

In-vivo models of *S. scabiei* infestation provide an extremely valuable opportunity to undertake longitudinal study of the disease. The cross infestation of rabbits with canine mites provided the first such model [3]; however, the potential impact of the nonnatural host on host–parasite interactions is unknown. Natural host models of scabies have recently been developed. Experimental infection in sheep confirmed the previous evidence that a host response to initial infection can be protective against subsequent challenge [13]; however, in Iberian ibex, the response appeared to vary with the host sex [14]. Vaccination with soluble scabies mite proteins in goats [15] and with recombinant scabies mite tropomyosin in rabbits [16▪] both failed to protect against subsequent infestation. A natural host model of scabies in pigs was maintained over 5 years and 10 animal cohorts, using a single population of mites [17]. These models represent valuable research tools to further investigate host–parasite interactions and to trial novel therapeutic agents, although as large animal models they can be expensive and logistically difficult and thus experiments needs to be extremely targeted.

HOST SPECIFICITY OF SCABIES MITES

Host specificity and cross infestivity of scabies mites have been an area of ongoing investigation. No stable morphological differences between scabies mite populations have been identified despite detailed study [18]. Early cross infestation experiments involving the transfer of dog mites to hosts, including mice, rats, guinea pigs and pigs, were only successful in establishing long-term infestation in rabbits [3]. This provided to some degree the evidence of host preference and suggested that physiological differences may exist between scabies mites associated with different host species [3]. This was further supported by the studies that showed that different host-associated scabies mites produce proteins which are immunologically recognized by other host species, as well as some proteins which are only recognized by their natural host [19]. Several subsequent studies using regions of rRNA genes failed to distinguish host-associated populations on the basis of genotype, although some evidence of geographic association was observed [20–23]. However, studies using microsatellite markers provided evidence that interbreeding of scabies mites from sympatric human and canine hosts was rare, even when living in close contact in a single household [24,25].

Several recent studies of mite genetics have continued the focus on the question regarding the host specificity of scabies mites. A recent microsatellite study analysed the genetic diversity in a wild animal population over an 11-year period. They demonstrated temporal genetic stability, with a lack of gene flow between mites from sympatric host populations [26]. These data concord with another recent study comparing scabies mites from populations of wild animal hosts in Europe. Mites were found to cluster into herbivore, carnivore and omnivore host-associated populations and supported previous conclusions that scabies mites are not a panmictic population, even within a geographic location [27]. However, the 'host taxon' law concluded from these studies did not hold in a further study that showed an absence of gene flow within sympatric herbivore and carnivore populations, with closer similarity between mites from individual carnivore and herbivore host species. They concluded that prey to predator transfer of mites may account for this [28]. The data to date clearly point to limited gene flow between some host-associated populations of mites. Geographical and host behavioural factors as well as mite adaptation to host physiological differences likely all contribute to this. Knowledge of the scabies mite population structure can help to understand the patterns of disease transmission and thus inform disease control efforts. Indeed, this knowledge has recently been used to infer the source of scabies mite infesting wildebeest imported to the United Arab Emirates from Tanzania [29].

HOST DEFENCE EVASION MECHANISMS

The peritrophic matrix is found in the gut of many arthropods, where it plays roles in enhancing digestion and in protecting the gut from physical and chemical damage. A recent study demonstrated the presence of peritrophin, a major component of the peritrophic matrix, in the scabies mite gut where it colocalized with serum molecules including complement [30▪]. Immunoblotting indicated that mannan-binding lectin, the recognition molecule of the lectin pathway of human complement activation, specifically binds to glycosylated scabies mite peritrophin. The presence of the complement component C9 was also detected in the scabies mite gut; however, the presence of the terminal membrane attack complex (C5b-9) could not be detected. This indicates that despite the likely activation of the lectin pathway by the binding of mannan-binding lectin to mite peritrophin, mechanisms within the mite gut preclude the formation of the membrane attack complex, thus protecting against complement-mediated damage [30▪].

Inhibitory molecules that block complement components are produced by many pathogens including arthropods such as ticks (reviewed in [31]). It appears that scabies mites may have developed several mechanisms to achieve this. Members of a large family of scabies mite inactivated serine proteases (SMIPP-Ss) produced by the scabies mite [32] were shown to be capable of inhibiting all three complement activation pathways [33,34▪]. In addition, serine protease inhibitors (serpins) expressed by the mite were also found to be capable of inhibiting complement activation pathways [34▪,35▪]. The SMIPPs and serpins were localized to the mite gut, where complement activation is likely to occur. In addition, they were also found in mite faecal pellets raising the possibility that they may also have an effect in the localized area of the mite burrow, providing conditions conducive to the growth of pathogenic skin-associated bacteria [33].

THE SCABIES MITE AS PART OF A COMPLEX SKIN MICROBIOME

Epidemiological data show a strong link between infestation with scabies mites and infection with pathogenic bacteria such as group A *Streptococcus* in humans (recently reviewed in [36,37]). Group A *Streptococcus* infection secondary to scabies infestation is thought to cause significant sequelae such as acute rheumatic fever and rheumatic heart disease in humans. A recent study demonstrated that the complement inhibitors produced by the scabies mite promote the growth of group A *Streptococcus* in whole human blood *in vitro* [34▪]. This suggests that localized complement inhibition in the mite burrow by excreted mite products play a role in the development of pyoderma in scabies mite infested skin. Likely, this mechanism would also promote the growth of other bacteria within mite-infested skin and further mechanisms contributing to pathogenicity can be expected. This emphasizes that scabies mites infesting a host can be considered to be a part of the complex environment of the whole skin microbiome. The skin bacterial microbiome plays a major role in skin biology and can alter during disease events. Enormous progress has been made using high throughput sequencing in defining the bacterial skin microbiome of humans, circumventing the challenges involved in isolation and cultivation of many cutaneous bacterial species (reviewed in [38▪]). However, in most conditions the skin microbiome includes further microbes apart from bacteria – archaea, fungi, viruses and mites. Very little is known on how the entire microbiome interacts with their human host and with each other and what determinants there are to shift the relationships from a healthy into a diseased host state. Understanding these principles should ultimately guide appropriate treatment.

Several studies have recently addressed the role of mites in the skin microbiome. Mites are commonly viewed as intruders that provide an opening for other pathogens. However, this is not always the case. A mutualistic relationship between feather mites and a large range of birds was recently proposed, in which the avian hosts benefit from increased diversity and abundance of feather mites clearing bacterial loads from skin, feathers and eggshells, while the mites benefit from secretions from the bird's skin glands and the consumption of bacteria [39]. However, mites that penetrate the skin are generally parasitic to their host and promote the growth of associated bacteria. *Dermanyssus gallinae*, the hematophagous poultry red mite, is a serious pest of poultry and a potential pathogen vector causing a significant health problem in the poultry industry [40]. It acts as a biological vector of *Salmonella*, promoting bacterial multiplication within their intestinal system and through transovarial as well as transstadial passage [41]. To understand the diversity of microbiota associated with *D. gallinae*, the first microbiota analysis of the whole internal bacterial community of these mites was recently undertaken [42]. Similarly, *Demodex* mites may play a role in promoting bacteria that cause rosacea, a skin disease known to affect between 5 and 20% of the world's population (reviewed in [43]). A total of 80% of a cohort of 26 patients with erythematotelangiectatic rosacea showed immunological reactivity to proteins from *Bacillus oleronius* [44], a

bacterium previously isolated from *Demodex* mites obtained from a rosacea patient [45]. Further work demonstrated that several proteins produced by *Demodex*-associated *B. oleronius* activate neutrophils to migrate and to produce inflammatory cytokines [46]. Another study suggested a possible link between the high density of *Demodex* mites on the eyelashes of ocular rosacea patients and the development of corneal ulcers because of the exposure of corneal epithelial cells to *B. oleronius* proteins [47].

The diversity of bacteria associated with *S. scabiei* has not been investigated in depth and it is unknown whether *S. scabiei* relies on obligatory endosymbionts for survival. Molecular mechanisms have been discovered by which scabies mites may directly affect the local bacteria population [34▪], thereby potentially causing serious secondary infections. Consequently, a clear definition of the mite-associated microbiome and the extensive characterization of molecular interactions within the mite–bacteria–host relationship is needed. Such studies would contribute to our understanding of the pathogenic processes that occur and guide the development of novel intervention strategies against scabies and associated pyoderma.

FROM MITE GENETICS TO MITE GENOMICS

Genomic and transcriptomic studies are an invaluable strategy to investigate fundamental aspects of mite biology, host–parasite interactions and pathogenesis. The arthropods are the most species rich and morphologically diverse group of animals, and their diversity is paralleled by the wide array of habitats they exploit. Despite this, detailed physiological data on these organisms remains sparse. Of the estimated more than half a million species of Acari (mites and ticks) [48], the genomes of only a small number have been investigated to date (tick genomes). A lack of available genome sequence data is hampering further research of important mite species. The publication of a preliminary genome survey of the honey bee mite *Varroa destructor* [49] and, more recently, the first genome sequence of a chelicerate organism, that of the two spotted spider mite *Tetranychus urticae* [50▪▪], represent the advent of mite genomics. *T. urticae* has one of the smallest known invertebrate genomes at approximately 90 Mb, and genome sequencing resulted in 640 scaffolds covering 89.6 Mb [50▪▪].

Using a quantitative PCR-based method, the genome size of *S. scabiei* was recently estimated to be 96(±7) Mb [51▪]. The genome size estimate of *S. scabiei* female mites was not significantly different to that estimated from mixed life stages, which concords with the previous genetic evidence that haplodiploidy, or other forms of polyploidy, is not a feature of *Sarcoptes* [25]. The chromosome number of scabies mites was determined to be 17 or 18 in individual eggs, suggesting a possible XO sex determination mechanism [51▪]. A similar genome size was estimated for the sheep scab mite *Psoroptes ovis* [86 Mb (±2)]. Free-living organisms have been shown to have larger genome sizes than closely related parasitic counterparts [52▪]. Consistent with this, the free-living house dust mite *Dermatophagoides pteronyssinus* was found to have a larger genome than *S. scabiei* or *P. ovis*, estimated to be 151 Mb for female mites and 218 Mb for male mites [51▪]. The reason for the larger size estimate in males is not understood at this point.

The recent sequencing of the first chelicerate genome, the determination of the genome size of *S. scabiei* and the availability of mites from natural host models indicates that the sequencing of the scabies mite genome is now a realistic goal. Genome sequencing of scabies mites from human and pig infestations has recently commenced (D. C. Holt, K. Fischer, E. Mofiz, A. T. Papenfuss, personal communication). Genome and transcriptomic analysis will allow the investigation of fundamental aspects of mite biology, host–parasite interactions and pathogenesis. Ultimately, a comparative genome analysis approach is planned between related free living and parasitic astigmatid mites. Such an approach will likely detect genomic differences underpinning the very different biological niches of related mite pathogens, as was recently demonstrated for related parasitic and free-living protozoans [52▪]. This will provide the much-needed information infrastructure to guide productive paths of future research, with the aim of improving treatment and control of this ubiquitous pathogen.

CONCLUSION

Scabies can now be considered to be a complex interaction between host, parasite and their associated microbiomes. Understanding the mechanisms which underlie these interactions is critical to improving the treatment and control of this ubiquitous disease. Recent advances described here furthered our understanding of host–parasite interactions and developed natural host models that together provide a foundation on which future research can be based with the aim of developing specific strategies against this parasite. In addition, sequencing of the scabies mite genome will likely provide further insights into the fundamental aspects of mite biology.

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Conflicts of interest

There are no conflicts of interest.

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