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Invited Review

Parasitic mites of medical and veterinary importance – is there a common research agenda?

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ABSTRACT

There are an estimated 0.5–1 million mite species on earth. Among the many mites that are known to affect humans and animals, only a subset are parasitic but these can cause significant disease. We aim here to provide an overview of the most recent work in this field in order to identify common biological features of these parasites and to inform common strategies for future research. There is a critical need for diagnostic tools to allow for better surveillance and for drugs tailored specifically to the respective parasites. Multi-'omics' approaches represent a logical and timely strategy to identify the appropriate mite molecules. Recent advances in sequencing technology enable us to generate *de novo* genome sequence data, even from limited DNA resources. Consequently, the field of mite genomics has recently emerged and will now rapidly expand, which is a particular advantage for parasitic mites that cannot be cultured in vitro. Investigations of the microbiota associated with mites will elucidate the link between parasites and pathogens, and define the role of the mite in transmission and pathogenesis. The databases generated will provide the crucial knowledge essential to design novel diagnostic tools, control measures, prophylaxes, drugs and immunotherapies against the mites and associated secondary infections.

1. Introduction

Among the Chelicerates, the Acari (mites and ticks) represent the largest and most diverse taxon, with an estimated 0.5–1 million species in total. Of over 48,000 species described to date (Halliday et al., 2000), the vast majority are mites, with ticks accounting for approximately 1,000 species. Mites inhabit fascinating combinations of diverse ecological niches and lifestyles, ranging from free-living, predatory or plant-feeding, to obligate parasitic. There are major agricultural mite pests such as the free living cosmopolitan plant feeding spider mite *Tetranychus urticae*, which is known to feed on more than 1,100 plant species. Free living allergy-causing dust mites are likely the best studied acarid pathogens. An estimated 10–15% of individuals in the Western world suffer from asthma (Basagana et al., 2004), with approximately 85% of them likely having an allergy to house dust mites (Thomas et al., 2010). Several parasitic mites, foremost scabies mites and mite vectors of scrub typhus, are also of major concern to human health, particularly in socioeconomically disadvantaged communities. In addition, scabies mites and the related sheep scab mites cause a considerable global burden of disease in livestock and wildlife. There are many more parasitic mites that are of medical and veterinary concern and which, taken together, represent a significant liability to both humans and animals. Despite this, apart from the relatively narrow focus on asthma-associated mite allergens, the research input into mite borne diseases is minute. This review features solely those parasitic mites that are clinically most relevant to humans and domestic animals, hence it presents the 'tip of the iceberg'. The true range of parasitic mites is much larger. As this emerging research field receives increased recognition, the picture may likely become more complete, yet more complex, in the future. With the aim to identify common research goals in this field, the focus of this review is to align the most significant parasitic mite species of medical and veterinary importance, with regards to their biology, the diseases they cause and the status of our knowledge about them.

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2. Parasitic mites of medical and veterinary importance

2.1. Scabies and mange

Scabies is a skin infestation caused by the obligate parasitic mite *Sarcoptes scabiei*. This mite burrows into the upper layers of the skin of a wide range of mammalian hosts, including humans, feeding on epidermal cells and serum (reviewed in Holt et al., 2013). Scabies affects both humans and animals, with different host-specific varieties (pathovars) of *S. scabiei* (Bornstein and Samuel, 2001), such as *S. scabiei* var. *hominis* from humans, *S. scabiei* var. *canis* from dogs and *S. scabiei* var. *suis* from pigs. Early studies reported on the limited capability of different pathovars to survive on non-natural hosts, although an ongoing infestation of dog mites on rabbits was established (Arlian et al., 1985, 1988b). More recent molecular epidemiology and phylogenetic studies (Alasaad et al., 2013) (also reviewed in Holt and Fischer, 2013; Alasaad et al., 2014) clearly showed host-specific mite populations. Importantly, no evidence of cross-transmission was identified between sympatric mite populations obtained from humans and dogs living in proximity (Walton et al., 1999, 2004b). Occasional infestations of humans with *S. scabiei* of animal origin have been reported but appear to be short-lived and self-limiting (Menzano et al., 2004; Bazargani et al., 2007).

2.1.1. Sarcoptes scabiei var hominis

Scabies is listed among the top 50 most prevalent diseases worldwide, with a global prevalence of 100,625,000 in 2010 (1.5% of the world population) (Hay et al., 2014). Scabies is one of the three most common skin disorders in children, together with tinea and pyoderma (Andrews et al., 2009; Vos et al., 2012), and imposes a considerable economic burden on individuals, families, communities and health systems (Fuller, 2013; Heukelbach et al., 2013). Owusu-Edusei et al. (2009) estimated the annual economic burden for scabies management as US $10.4 million (Owusu-Edusei et al., 2009). Recently the World Health Organization added scabies to the list of "Neglected Tropical Diseases", thereby recognising its impact on human health. The International Alliance for the Control of Scabies, a newly formed organisation, proposes to accomplish scabies control in vulnerable communities (Engelman et al., 2013).

The life cycle of *S. scabiei* has four parasitic stages (egg, larva, nymph and adult) and takes approximately 2 weeks. The adult female mite burrows into the stratum corneum and stratum granulosum of its host (Levi et al., 2011), where she lays two to three eggs per day. Burrowing is achieved using mouth parts, special cutting surfaces on the front legs, and enzymatic secretions. The mite releases allergenic metabolic products into the burrows, from where they diffuse into the underlying dermis to provoke strong hypersensitive reactions and intense itching. As a result, scratching and disruption of the upper epidermal protective matrix ensues, promoting infection by opportunistic bacteria. These can lead to serious health complications. In northern Australian remote Indigenous communities, very high rates of scabies-associated streptococcal and staphylococcal infections have been documented (Carapetis et al., 1997; Carapetis and Currie, 1996; Lin et al., 2009; Steer et al., 2009; Subramaniam et al., 2010). Consequently, in populations where scabies is endemic, severe sequelae such as acute rheumatic fever, rheumatic heart disease and acute post streptococcal glomerulonephritis have been reported (Carapetis et al., 1997; Carapetis and Currie, 1996; and reviewed in Hay et al., 2013).

The healthy host immune system is able to limit mite numbers in primary infestations to 10–20 adult mites, and with subsequent re-infestations mite numbers are reported to drop to less than five. Occasionally, the host becomes completely protected (Mellanby, 1944; Rodriguez-Cadenas et al., 2010). Recently, extracts derived from scabies mites have been shown to modulate cytokine expression by keratinocytes, fibroblasts, dendritic cells and peripheral blood mononuclear cells, thereby initiating inflammation (Arlian et al., 2004; Morgan and Arlian, 2010; Morgan et al., 2013). Crusted scabies, a severe manifestation of the disease, occurs in people with a non-protective immune response to the mite (Roberts et al., 2005) and is a rare manifestation characterised by hyperinfestation of the skin with thousands of mites/g of skin, often leading to sepsis and death. Increased localised skin IL-17 secreting T cells may play a critical role in the pathogenesis of crusted scabies development (Liu et al., in press) and, although the underlying mechanisms are still unknown, support a hypothesis that regulatory T cell function may be impaired. Crusted scabies mainly occurs in immune compromised individuals or in the elderly, and is frequently observed in nursing homes or institutions where they often act as core transmitters (Lokuge et al., 2014). Those affected suffer social stigma and often remain undetected and untreated for a long time, thereby presenting a hidden reservoir of parasites (Roberts et al., 2005; Currie and McCarthy, 2010).

Ten years ago the molecular biology of scabies was largely unexplored. Since then significant progress has been made on characterising a number of *S. scabiei* antigens/allergens and determining their role in the mite as well as their role in immunopathogenesis (Mattsson et al., 2001; Pettersson et al., 2005; Mounsey et al., 2013). This has been possible in large part due to the generation of a cDNA database of approximately 43,000 cDNA sequences from scabies mites collected from a human patient (Fischer et al., 2003a). This database enabled the discovery of homologs to house dust mite allergens (Fischer et al., 2003a; Holt et al., 2003, 2004; Dougall et al., 2005), genes implicated in drug resistance (Mounsey et al., 2006, 2007, 2010b; Pasay et al., 2006, 2008), proteins with immunodiagnostic potential (Harumal et al., 2003; Walton et al., 2010; Jayaraj et al., 2011; Rampton et al., 2013), and families of molecules which may have a role in pathogenesis (Beckham et al., 2009; Bergstrom et al., 2009; Fischer et al., 2009; Holt et al., 2003, 2004; Mika et al., 2011, 2012a, 2012c; Mahmood et al., 2013). *Sarcoptes scabiei* recombinant proteins are now being produced that are leading to advances in understanding the biology of the mite and protective and aberrant immune responses observed in scabies, and potentially novel therapeutic avenues for patients (Walton, 2010; Zhang et al., 2012; Gu et al., 2014a; Liu et al., 2014).

Upon infecting the epidermal layers, the mite would be exposed to serum components that diffuse in from underlying dermal microvasculature (Rapp et al., 2006). The mite ingests these components (Rapp et al., 2006; Bergstrom et al., 2009; Walton et al., 2010; Mika et al., 2011) and consequently must defend its intestinal system against the onslaught of these host defence systems. Complement is a crucial and first line host defence system that is activated upon contact of a microbe with host body fluids. It is a complex network involving approximately 40 proteins. Every successful parasite must have defence mechanisms against this system. Similar to many haematophagous arthropods, the scabies mite has evolved a sophisticated arsenal of mechanisms to avoid complement-mediated gut damage. Mite complement inhibitors, specifically serpins (Mika et al., 2012a) and Scabies Mite Inactivated Serine Protease Paralogs (SMIPP-Ss) (Bergstrom et al., 2009; Reynolds et al., 2014) have been identified as molecules the mite may use to overcome the host defence. Members of the extensive family of SMIPP-Ss have been shown to inhibit the activation of host complement (Bergstrom et al., 2009), particularly the lectin pathway (Reynolds et al., 2014). Scabies mite serpins have been documented to reduce the deposition of several complement components, thereby blocking the human

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