Scabies and bacterial skin infections at a molecular level

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Aboriginal and Torres Strait Islander peoples are nearly 20 times more likely to die from acute rheumatic fever (ARF) and rheumatic heart disease (RHD) than individuals from the wider Australian community. ARF and RHD as well as high rates of renal disease have been clearly linked to scabies infestations as the major driving force of streptococcal pyoderma in children of Indigenous communities, underlying 50 to 70% of all skin infections. In addition, patients are facing mite resistance against current anti-scabetic therapeutics. Community-based initiatives have been recently expanding and today form the major existing body of knowledge surrounding scabies. Critical biological questions, however, remain unanswered, due to the lack of biomedical research in the area. In the context of the current failure to overcome the social dimensions of Indigenous health issues, molecular approaches that have only now become possible may well lead to vaccines or other clinical interventions and hence to an improvement of the situation.

Impact of scabies

Scabies is a transmissible parasitic skin infestation caused by the mite *Sarcoptes scabiei* (Figure 1). It is common worldwide and spreads rapidly under crowded conditions, such as those found in institutional settings, for example, prisons and long-term care facilities. Although scabies is unusual in urban Australia, it is currently endemic in remote northern and central Australian Aboriginal communities and it remains a major public health problem in these socially disadvantaged communities. Infestation occurs when the adult female mite burrows in the lower stratum corneum layers of the epidermis (Figure 2). Rates of crusted scabies (hyperinfestation associated with high mortality) in these communities are amongst the highest in the world and, despite treatment, relapses are frequent.

Pruritic scabies lesions facilitate opportunistic bacterial infections, particularly by Group A streptococci (GAS) and staphylococci. Recent data obtained through the East Arnhem Regional Healthy Skin Program suggest that over 70% of 2-year-old children in remote Aboriginal communities have been infected with scabies, most of them acquiring their first infection as infants. Importantly, these numbers dramatically parallel the rates of observed streptococcal skin infections in over 80% of these children (Figure 3). Streptococci infections cause significant sequelae (cellulitis, sepsicaemia, acute glomerulonephritis and chronic renal disease) and the increased community streptococcal burden has lead to the most extreme levels in the world of ARF and RHD in Australia’s Indigenous communities. Emerging resistances to the currently available anti-scabetic therapeutics – permethrin and ivermectin – emphasise the need to identify novel potential targets for novel chemotherapeutic and/or immunological intervention.

New insights into the link between scabies and bacterial infections

It has long been thought that GAS pharyngitis alone was responsible for ARF and RHD, a dogma that underpinned prevention guidelines and vaccine research, but was based on studies mostly conducted in temperate climates, where GAS skin infection is uncommon. Recently, Australian researchers postulated a new hypothesis most likely to be more in line with the situation in tropical regions of Australia. The epidemiology of ARF in Aboriginal communities of central and northern Australia clearly challenges the established view as throat carriage rates of GAS are extremely low (usually 1% of...
to 5%) and symptomatic GAS pharyngitis is rare. Instead, pyoderma (defined as bacterial infection of the skin) is the major manifestation of GAS infection. Typical ‘rheumatogenic’ strains observed in pharyngitis do not occur. More commonly group C and G streptococci are isolated from the throats of Aboriginal children and have been shown to exchange key virulence determinants with GAS. The large reservoir of GAS strains usually present on the skin may allow constant genetic reassortment, with the development of new epitopes, allowing evasion of host defences and the sharing of virulence factors. In conclusion, GAS pyoderma and/or non-GAS infections are most likely the driving forces behind ARF and renal disease in Australian Indigenous communities, with the skin being the major interface of transmission.

Parasitic skin diseases like pediculosis, scabies, fungal disease, cutaneous larva migrans and myiasis occur in all climates, but are especially common in the tropics. As well as climate many other underlying factors, such as inadequate housing and overcrowding, most certainly are significant. Consequently, while the prevalence of scabies in the general population of Australia is rather low and outbreaks are confined quickly, scabies frequencies can be extremely high and difficult to assess in our nation’s vulnerable groups in resource-poor settings, which most Indigenous neighbourhoods are.

In Australia’s Indigenous population, skin damage due to scabies infestations seems to be a major link in the puzzle of ARF pathogenesis. A great amount of epidemiological evidence has been accumulated establishing the fact that scabies is linked to pyoderma (reviewed in 21-24). In scabies infections pruritus almost always occurs and scratching leads to secondary infection, with bacteria usually present on the skin. Studies in which the prevalence of pyoderma was assessed before and after the control of scabies provide valuable clues. For example, in a control program in the Solomon Islands, the prevalence of scabies in children decreased from 25% to 1% and that of the pyoderma from 40% to 22% 25. Studies in Australia 19, 26

Figure 2. A schematic illustration featuring a female scabies mite burrowing in the upper epidermis. Arrows indicate key players of scabies and associated bacterial skin infections: Scabies mite defence (gut and faecal proteins, such as Scabies Mite Serpins, Sar s3, SMIPPs and cysteine proteases). Host response (immunoglobulins, complement, coagulation factors, host proteases). Bacteria entering the skin. Picture credit: Andrew A Erwin.
In Focus

indicate that in Indigenous populations up to 50% of pyodermas were caused by superinfected scabies. Here community-based programs aimed at eradicating scabies in endemic settings have had at least temporally a considerable impact\textsuperscript{26-29}. However, more recent data emerging from the East Arnhem Regional Healthy Skin Program emphasise once again the strong link between scabies and pyoderma and the urgency for attendance\textsuperscript{30}.

Both pyoderma and parasitic skin diseases, such as scabies, have had a low priority on the health agenda and have previously been ignored by healthcare providers. However, especially in combination, both conditions are responsible for important sequelae and have an impact beyond that of an annoying skin problem. Clearly scabies and pyoderma demand considerably more commitment from the wider research community, including basic scientists and from the healthcare providers. New understanding of the pathogenesis of ARF coupled with a new understanding at the molecular level could have an immediate effect on primary prevention strategies and vaccine development.

In search of new target molecules for scabies intervention

Despite the alarming figures, scabies remains a truly neglected infectious disease. The scarcity of molecular data on scabies is due to the difficulty in obtaining sufficient numbers of mites. The parasite burden in an average patient is generally very low and no \textit{in vitro} culture system to grow human mites is available.

Addressing this problem, we generated cDNA libraries\textsuperscript{30-32} from scabies mites picked from the bedding of severe crusted scabies patients. In collaboration with the AGRF (Australian Genome Research Facility Ltd) and funded by a National Health and Medical Research Council (NHMRC) Medical Genomics Grant, we created a public database of 43,776 sequences, which provides for the first time a substantial amount of molecular data on this parasite and secures a solid basis for recombinant biology.

From this resource we have discovered multigene families of serine and cysteine proteases\textsuperscript{33, 34} homologous to the group 3 and group 1 major allergens produced in the gut of scabies, mite-related astigmatid house dust mites\textsuperscript{35, 36}. These mite gut proteases are involved in the digestion of proteins ingested

Figure 3: Presentations (A) for scabies and (B) for skin sores (any sores located on the skin or other presumed bacterial infections of the skin including boils, carbuncles, abscesses, ulcers and pustules) within 2 years in two remote East Arnhem Land communities. Source: Clucas, D. \textit{et al}\textsuperscript{37}.
from the skin and hence offer an avenue for interfering with parasite establishment. We have recently characterised a scabies mite gut serine protease (Sar s 3) that appears to play a pivotal role in digesting skin proteins – an excellent candidate for the development of therapeutics to combat scabies [manuscript in review].

Unexpectedly, the scabies mite produces and excretes into the host epidermis an additional set of 32 closely related gut proteins also belonging to the SI-like serine protease family. However, due to mutations in the catalytic triad and considerable structural rearrangements, these have no proteolytic function but have instead evolved into potent inhibitors of each of the three pathways of the human complement system. We named these proteins SMIPPs (Scabies Mite Inactivated Protease Paralogues). SMIPPs are only one of several strategies that the mite has invented to overcome host defences. We now have evidence that there are at least two other multigene families of scabies mite molecules that can inhibit each of the three complement pathways [unpublished]. Interestingly, Roberts et al. have reported markedly altered immune function in many patients with crusted scabies. In particular, low complement levels were reported markedly altered immune function in many patients pathways [unpublished]. Interestingly, Roberts et al. have reported markedly altered immune function in many patients with crusted scabies. In particular, low complement levels were difficult to explain, since a large inflammatory response would usually produce hypercomplementaemia. Our current studies may provide more detail towards this problem in the future. It is also likely that other host defence functions (Figure 3) may be inhibited by scabies mite proteins. Such inhibition of host defences concentrated in the microenvironment of the scabies mite burrows may well be utilised to the advantage of bacterial pathogens such as GAS. We are currently refining evidence that supports this hypothesis. This may possibly be the way forward to a new generation of approaches to scabies control.

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References
20. McDonald, M.I. et al. (2007) Molecular typing of Streptococcus pyogenes from remote Aboriginal communities where rheumatic fever is common and pyoderma is the predominant streptococcal infection. Epidemiol. Infect. 135, 1398-1405.

A Bio for Dr Karin Fischer appears on p. 168. Professor David Kemp, PAA, recipient of the Order of Australia Medal in 2008, has had a distinguished career over the last 30 years, focusing on molecular aspects of malaria, initially at the Walter and Eliza Hall Institute in Melbourne, expanding to include the first molecular studies on scabies mites after moving to the Menzies School of Health Research in Darwin and now continuing his work at the Queensland Institute of Medical Research.