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Editorial

Biofilms, Chronic Infection and the Host-Pathogen Relationship

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Editorial

Biofilms develop where there is a liquid or solid and air interface meaning that they form ubiquitously within the human body. Consequently, biofilms are often a feature of infection, in particular recurrent or chronic infections such as non-healing wounds, recurrent urinary tract infection and chronic lung infection (such as that observed in cystic fibrosis). It is well established that biofilms are inherently more resistant to antimicrobial treatments and they have been shown to tolerate doses of up to 1000 times greater than planktonic bacteria [1]. In addition to offering protection from antimicrobial treatments and other environmental stresses, the exopolysaccharide layer of the biofilm shields microorganisms from the immune system. Therefore, biofilm-associated infections are difficult to clear and present a considerable problem to both the clinician and the host. These problems lie beyond antibiotic resistance alone and are underpinned by complex interactions between host- and pathogen that drive a number of evolutionary changes within the biofilm population.

Analysis of biofilms from chronic wound infection has revealed over 300 microbial species comprised primarily of aerobic bacteria with smaller numbers of anaerobic bacteria and fungi [2,3]. Despite the seemingly high number of microorganisms within chronic infected wounds, over time diversity diminishes as a result of succession, resulting in the emergence of a much smaller number of dominant species. A similar situation is observed in the cystic fibrosis lung where over a period of years *Pseudomonas aeruginosa* displaces co-habiting microbiota resulting in severe lung infection, associated with a high rate of mortality [4]. Persisting within the host for time periods ranging from months to years requires biofilm microorganisms to co-exist with the host. Bacteria have evolved a number of mechanisms that allow them to circumvent immune detection and subsequent elimination, many of which are driven by the host environment.

It is understood that the biofilm lifestyle enables regulation of a number of immunological responses, including in the case of chronic wounds, diminished healing and re-epithelialisation [5,6]. Several cytokines associated with inflammation and maintenance of chronicity have been identified as specific targets. The regulation of inflammatory cytokines by biofilm bacteria has been described extensively using *Staphylococcus aureus* as a model organism. *In vitro* experiments have examined the change in the inflammatory response of human keratinocytes exposed to conditioned media derived from both biofilm and planktonic bacteria. Global expression analysis using microarray, supported by ELISA demonstrated that IL-6, IL-8, TNF-α and CXCL2 is produced by keratinocytes in response to biofilm, but not planktonic cells indicating that bacterial biofilms have the capacity to promote and maintain a prolonged inflammatory response such as that observed during chronic infection [7]. Therefore, wound chronicity perpetuated by disruption of normal repair mechanisms, is facilitated at least in part by the infecting microbial population.

In addition to altering the inflammatory response during infection, biofilm bacteria can also attenuate the immune response, thus evading clearance and persisting within the host. *Streptococcus pneumoniae* which is a common coloniser of the human nasopharynx survives as a biofilm. Front-line defences to *S. pneumoniae* infection rely on complement activation and subsequent phagocytosis by neutrophils. Comparative analysis of biofilm and planktonic *S. pneumoniae* exposed to C3b indicates that deposition of C3b is significantly diminished for biofilm. This suggests that the biofilm lifestyle allows *S. pneumoniae* to avoid recognition by the complement system [8]. Furthermore, recognition by Clq and CRP is also diminished for biofilm, confirming that the biofilm lifestyle can also impede activation of the classical complement pathway. With such strategies as these, it is no surprise that biofilms persist within the human host.

From the perspective of long-term or chronic infection, immune evasion allows prolonged colonisation of the host and invariably bacteria begin to co-evolve within the host environment. Consequently, microorganisms start to become host-adapted [9,10]. The host environment is highly selective and demands constant optimisation of bacterial regulatory networks to ensure survival of the microbial population. The cystic fibrosis lung serves an excellent host system in which to assess host-adaptation and has been extensively studied in this regard using *P. aeruginosa* as a model. Analysis of temporal genetic changes that mediate successful long-term lung colonisation have led to the discovery of several conserved mutations associated with host-adaptation [11]. Critically these mutations occur within a number of sigma factor encoding genes indicating significant regulatory network remodelling as a consequence of host adaptation. Therefore, whilst biofilm organisms might shape the host response to infection, the host reciprocally impacts the bacterial population. This phenomenon, essentially an evolutionary arms race, sees both host and pathogen evolve together to reach an uneasy balance that enables both to co-exist.

Therefore, to effectively control and ultimately resolve chronic infections attention must be paid both the microbial community and to the host. The former is often overlooked by traditional diagnostic microbiology. The shift to chronicity is in part facilitated by critical

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bacterial colonisation, followed by the establishment of a biofilm, and eventual diminution of species diversity as the population adapts to its environment. Thus finding the most appropriate and efficacious treatments requires acknowledgement of the dynamic microbial population.Molecular analysis of microbial populations and next generation sequencing are broadening our understanding of the genetic changes that occur as pathogens adapt to their host, but translating these into tangible strategies to prevent or resolve chronic infection remains to be a challenge for the future.

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