Lay Abstract

Pathogens are biological agents that can cause disease in a host, such as viruses, bacteria, fungi and parasites. They must overcome many obstacles in order to persist within their host. The first challenge for pathogens is to cross the physical barrier of the skin in order to gain entry. Damage to the skin breaches this first obstacle providing the opportunity for invasion. Inflammation is the body's response to damage/infection, and is the next big challenge for any pathogen to overcome. The inflammatory process recruits a multitude of immune cells to the site of infection via pro-inflammatory molecules, like an army responding to a siren to protect its boarders, where they then detain and eliminate the enemy. And, like in any war collateral damage occurs, which in this case is in the form of host vascular and tissue damage. Once the enemy or pathogen is effectively cleared, the immune cells or soldiers retreat, allowing the healing process to begin. This two pronged approach of inflammation is crucial in protecting the host from infectious diseases; however prolonged inflammation can help to escalate the damage caused by these diseases, potentially threatening the life of the host.

Scientific Abstract

The host is an extremely hostile environment to an invading pathogen, and inflammation is a key component of that hostility. Although intrinsically protective, inflammation is at the core of pathogenesis and a fine balance is required to keep inflammatory processes beneficial. Platelets play an important role as immune cells and also in inflammation, facilitating in the recruitment of other immune cells via the release of pro-inflammatory cytokines and the expression of adhesion molecules. They are also important sources of immune-regulatory cytokines. Platelets have been implicated in protecting the host from malaria infection via the direct killing of parasites. However, due to inflammatory induced damage, platelets can also have a role in causing serious cerebral malaria. Systemic inflammation can influence and result in unnecessary encephalitis, which is associated with neurological dysfunction and is a major cause of death worldwide. In Japanese encephalitis virus infection, devastating encephalitis has been linked to destructive host inflammatory processes increasing the permeability of the blood brain barrier. Although inflammation is crucial in protecting the host from potentially life-threatening pathogens, regulation and a time-dependent action of inflammation is equally as important.

changing the nature of the endothelium, causing vasodilation and attracting immune cells. These three actions of inflammation are key in mounting an effective immune response. The ability of immune cells to be able to travel to the site of infection in the circulation and then squeeze across the endothelium is crucial, as without this protection cannot occur (Muller, 2013). This is referred to as transepithelial migration (TEM) and although necessary, it is at the heart of immunopathogenesis. Hence, this mechanism is desired only locally at the site of infection, and nowhere else in order to confine pathogenesis to specific locations. However; local inflammation does induce a systemic increase in plasma inflammatory mediators such as complement proteins. Complement has powerful antimicrobial effects required to effectively eliminate many pathogens, e.g. *Pseudomonas aeruginosa* (Zhang et al., 2009). Acute inflammation is crucial in pathogen clearance; conversely chronic or misplaced inflammation can cause immunopathogenesis which can be worse than the damage caused by the invading pathogen.

The role of platelets in inflammation

Platelets exhibit a multitude of functions, including their ability to mediate hemostasis and their action as immune cells. As mentioned, there are sentinel cells in the skin, but platelets are the sentinel cells of circulation. They are one of the first cells to accumulate at the site of vascular damage, due to injury or infection, and their role in inflammation is becoming more appreciated (Morrell et al., 2014). Platelets are formed from megakaryocytes and are the smallest yet most abundant cells in circulation, at 150-400$\times10^9$ cells/Litre (Klinger and Jelkmann, 2002). Therefore although they are small their sheer numbers along with the fact they can directly interact with infectious agents, other immune cells and vascular endothelium, enables them to exert diverse and large scale inflammatory effects (figure 2).

Each platelet contains over 60 granules, which are divided into specific populations; α-granules, dense granules and lysosomal granules (Morrell et al., 2014). Mass spectrometry studies have shown that α-granules alone contain hundreds of bioactive proteins that can be released during platelet stimulation (Maynard et al., 2007). α-granules are the largest granules storing proteins necessary for a plethora of different functions in both the pathogen destructive phase of the inflammatory response, and subsequent inflammatory resolution followed by healing (figure 2). Lysosomal granules contain digestive enzymes including those with antimicrobial properties, but these enzymes can unfortunately also facilitate vascular damage, often aiding in the pathogenesis of infectious diseases. Dense granules release factors that are associated with recruiting other platelets (Rendu and Brohard-Bohn, 2001).