Streptococcal M1 Strikes by Neutralizing Cathelicidins

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Virulent group A streptococci have become a serious threat, with the emergence of the hypervirulent lineage M1T1. In this issue of *Cell Host & Microbe*, LaRock et al. (2015), uncover a role for the streptococcal M1 protein in neutralizing a key human antimicrobial peptide, cathelicidin.

Since the mid-1980s, group A streptococci (GAS) have reemerged as a cause of severe invasive infections, such as septicaemia, puerperal sepsis, soft-tissue infections including necrotizing fasciitis, and streptococcal toxic shock syndrome. Despite increased awareness and better treatment of the most severe disease manifestations, the mortality rate remains high, often exceeding 50%. To date, more than 150 different M protein sequence types (emm types) have been described for GAS. Although the most severe forms of invasive GAS infections, streptococcal toxic shock syndrome and necrotizing fasciitis, can be caused by a large number of emm types, they are particularly associated with *emm1* (M1). One example of the rapid progress of M1 infections was recently reported for three cases of fulminant hemorrhagic pneumonia in...
previously healthy patients (Santagati et al., 2014). These patients developed hemoptysis and dyspnea, and all three died within 12 hr from massive pulmonary bleeding. Postmortem analysis showed that the illnesses were caused by emm1 strains. This clinical picture suggests a pathogen that is highly toxic and tissue damaging and resistant to early innate clearing systems, thus allowing unrestricted growth.

This epidemic clone emerged in a step-wise manner from a less virulent M1 ancestor culminating in the 1980s by acquisition of a large chromosomal region encoding the secreted toxins NADase and streptolysin O (Nasser et al., 2014). This genetic event has been suggested to act as the key driver for increased toxin production and enhanced infection severity of current M1 pandemic strains.

The M1 surface protein is not just a marker for this successful and highly virulent lineage. The protein itself has been shown to contribute to the intracellular survival of S. pyogenes in macrophages (Hertzén et al., 2010), and recently it was demonstrated that the M1 protein triggers chemokine formation, neutrophil infiltration, and lung injury in a process dependent upon the transcriptional factor NFAT (Zhang et al., 2015).

In this issue, LaRock et al. (2015) demonstrate that the M1 protein triggers chemokine formation, neutrophil infiltration, and lung injury in a process dependent upon the transcriptional factor NFAT (Zhang et al., 2015).

Previously that equivalent, CRAMP. It has been shown another function—namely to mediate demonstrating that the M1 protein has yet another function including the regulation of immune cell activation and their migration, other functions in the regulation of immune cell activation and their migration, and in modulating many physiological processes that involve non-immune cells, such as activation of wound healing, angiogenesis, and cartilage remodeling.

LL-37 has also been suggested to play a role in the pathogenesis of psoriasis by acting as a T cell auto-antigen (Lande et al., 2014). Cathelicidins are primarily formed in neutrophils, but can also be produced by macrophages, mast cells, and keratinocytes. They are released as a pro-form that needs to be processed to generate biologically active peptide. Here, LaRock et al. (2105) demonstrate that emm1 strains sequester the pro-form of LL-37, as well as LL-37 itself, via a region on M1 localized close to the cell membrane. LL-37, binding to the M1 protein, appears specific as no binding was observed with defensins. Binding of pro-LL-37 is usually followed by its proteolytic cleavage, but this did not occur when sequestered by the M1 protein. This explains why emm1 strains become protected from the direct killing action of LL-37, but also from the innate activation functions of LL-37, such as stimulation of immune cell migration. Using a localized skin wound model, it was demonstrated that M1 strains give rise to similar sized lesions in wild-type and CRAMP−/− mice, suggesting that M1 expression protects against the local innate immune effects of cathelicidins.

There have been earlier reports showing that proteases expressed by a number of bacterial pathogens including GAS can degrade and inactivate antimicrobial peptides such as LL-37. GAS strains have been shown to secrete the SIC protease, and it was demonstrated that SIC from M1 strains was more potent in degrading LL-37 than other GAS strains (Fricks et al., 2003). GAS strains can also express GRAB, a surface associated protein that sequesters alpha(2)-macroglobulin, which is a major proteinase inhibitor of human plasma. Trapping of alpha(2)-macroglobulin by GRAB allows GAS to retain the normally secreted SpeB protease on its surface, which in turn can protect against killing by LL-37 (Nyberg et al., 2004). Finally, it has been demonstrated using M1 strains that LL-37 can directly bind to the histidine kinase sensor CsrS in the two-component system CsrRS, resulting in upregulation of a number of virulence-associated GAS genes (Velarde et al., 2014). It would be interesting to know if the sequestering of LL-37 by M1 contributes to this upregulation of GAS virulence. A detailed study on the exact mechanism for pro-LL-37 and LL-37 binding to M1 might give further insights into the intimate relationship between the emerging global pathogen GAS of emm1, and one of the early innate immune defense molecules, LL-37.

REFERENCES


