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Staphylococcus aureus and CCR5: unveiling commonalities in host–pathogen interactions and potential treatment strategies

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Abstract

Microbes that have acquired the ability to colonize and/or cause disease in humans must be able to both recognize and respond to host defenses to ensure their survival. For commensal microbes, adaptive strategies generally promote a balance between host immune defenses and bacterial maintenance, allowing asymptomatic colonization. Pathogenic microbes, on the other hand, tilt the balance in favor of the microorganism, leading to symptomatic illness and disease. Some microorganisms that are known to be asymptomatic colonizers of humans can cause serious disease upon gaining access to foreign sites and usurping immunological attack. The Gram-positive bacterium *Staphylococcus aureus* is one such microorganism.

This article will address recent advances in our understanding of *S. aureus* immune evasion with an emphasis on immune cell targeting. The prospects of this targeting in terms of understanding the evolution of *S. aureus* as a pathogen as well as its implications for future anti-*S. aureus* therapeutics, will be discussed.

CCR5: a common thread in immune cell targeting by pathogenic microbes

Approximately a third of the population is asymptomatically colonized by *S. aureus*; however, upon breaching its host ecological niche, the organism is capable of causing devastating disease. Its success in these foreign environments is attributed to a multifaceted attack on components of the host immune response. *S. aureus* produces numerous factors that impair the immune system, including antibody-binding proteins, proteases, immunomodulatory proteins, superantigens and immune cell-targeting cytolytic peptides and cytotoxins [1]. Each of these factors interacts with cells and/or molecules of the host immune system, perturbing their normal function and preventing bacterial clearance. In a recent study, the HIV coreceptor CCR5 was identified as a molecular target of the *S. aureus* bicomponent leukotoxin ED (LukED) [2]. CCR5 recognition by LukED promotes toxin

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binding to immune cells, allowing it to form pores in cellular membranes, ultimately leading to cell death [2].

Interestingly, CCR5 targeting appears to be a common trait among a number of pathogenic microbes. HIV is well known for its recognition of CCR5 on T cells. The HIV-encoded protein gp120 interacts with CCR5 to promote cell surface recognition, ultimately leading to viral entry [3–5]. Large dsDNA poxviruses, including vaccinia and myxoma virus, also use CCR5 to promote viral dissemination during infection, although the exact mechanism of action is not yet known [6,7]. In addition to CCR5 targeting by viruses, the protozoan pathogen *Toxoplasma gondii* uses CCR5 to manipulate dendritic cell function during infection. The production of cyclophilin 18 by *T. gondii* acts as a chemokine mimic for CCR5 and influences cellular signaling, which is presumed to benefit transmission from host to host [8].

Prior to studies of LukED, no known bacterial virulence factor had been found that directly targeted CCR5, although it had been previously postulated that *Yersinia pestis* might use CCR5 in its pathogenic processes. Support for this notion came from the supposition that the acquisition of a naturally occurring mutant allele of CCR5, $\Delta 32$ -CCR5, which renders individuals resistant to HIV infection [9,10], may have been selected for during a rapid and deadly event, such as plague [11]. This connection between CCR5 and *Y. pestis* pathogenesis was largely discounted when it was determined that CCR5 $^{-/-}$ mice were as susceptible to infection as CCR5 $^{+/+}$ mice [12]. Thus, identification of CCR5 as a receptor for LukED provides the first evidence of receptor recognition by a bacterial virulence factor. LukED targeting of CCR5 $^{+}$ cells appears to promote pathogenesis via the killing of immune cells central to infection resolution. Indeed, immune cells isolated from CCR5 $^{-/-}$ mice are fully protected from toxin-mediated killing [2]. These same CCR5 $^{-/-}$ mice display significantly reduced mortality upon systemic infection with *S. aureus* [2]. Thus, similar to HIV, the presence of CCR5 on host cells is critical for *S. aureus* pathogenesis.

The ability of viruses, protozoa and bacteria to use CCR5 to target the immune system is intriguing and opens interesting avenues for research into the coevolution of pathogens and their hosts. Regarding the pathogen, it is likely that a selective advantage is conferred by direct targeting of CCR5; one that is not provided by targeting other redundant chemokine receptors that perform similar biological functions. Regarding the host, acquisition of $\Delta 32$ -CCR5 does not appear to compromise normal host immunity, although it has been implicated in the severity of certain autoimmune conditions [13]. Loss of CCR5 in order to protect from deadly infection would thus appear to largely benefit the host, as the receptor does not seem to be critical for day-to-day immune homeostasis. Of note, however, is that while $\Delta 32$ -CCR5 can protect from certain infections (e.g., HIV) [14], it also negatively influences the outcome of other infectious diseases [15,16]. Thus, the appearance of $\Delta 32$ -CCR5 in the human population is not simply explained by its ability to confer resistance to multiple deadly infectious diseases. Until the dynamic roles of CCR5 in infection are fully elucidated, we remain limited in our predictions of the influence of the receptor on global human health and its evolution.

CCR5 & the immunological response to infection

A precise mechanism behind the reduction in mortality of CCR5^{-/-} mice during infection with LukED-producing *S. aureus* can be inferred through evaluation of CCR5⁺ immune cell subsets. CCR5 is present on the surface of macrophages, dendritic cells and some T cells, including subsets that are capable of producing IFN- γ , known as Th1 cells, or IFN- γ and IL-17, known as Th17 cells. Interestingly, recent immunological studies seeking to identify immune cell subsets critical for controlling *S. aureus* infection determined that both Th1 and Th17 cells play important roles in defense against *S. aureus* infection, as well as the development of adaptive immunity [17–19].

Recent studies imply that CCR5 recognition by LukED allows *S. aureus* to kill CCR5⁺ immune cells that are critical to *S. aureus* infection resolution in vivo, thereby enhancing virulence. In fact, the reduction in mortality of CCR5^{-/-} mice infected with *S. aureus* and that of wild-type mice infected with an *S. aureus* lukED mutant is identical [2,20]. The identification of a role for Th1/Th17 cells in the resolution of *S. aureus* infection, coupled with the influence of CCR5 and LukED on pathogenesis, implies a role for toxin targeting of these important T-cell subsets, the majority of which express high levels of CCR5 in vivo. By eliminating IFN- γ - and IL-17-secreting cells, the toxin would effectively blunt the response to acute infection [19]. However, a role for toxin targeting of CCR5-expressing antigen-presenting cells, such as macrophages and dendritic cells, cannot yet be discounted. Additional studies will provide a better picture of the contribution of CCR5⁺ cellular subsets to infection resolution and the influence of LukED cellular targeting on this process. Regardless, it is now clear that CCR5 plays a major role in the pathogenesis of *S. aureus* during murine systemic infection, and that both innate and adaptive immune cells contribute to the host response.

Future perspective: CCR5 antagonists as *S. aureus* therapeutics

The infection-resolution dynamics of CCR5⁺ immune cells and the influences of LukED in undermining this process are still being investigated. However, given that CCR5^{-/-} mice are largely resistant to *S. aureus* systemic infection, we propose that blocking CCR5 could prove beneficial in treating *S. aureus* infections. CCR5 antagonists, including the clinically used drug maraviroc, are already being used to treat HIV infection. These antagonists completely block LukED cytotoxicity towards immune cells [2]. Therefore, CCR5 antagonist efficacy studies for the treatment of *S. aureus* infections are within reach, particularly for drugs such as maraviroc. We envision that the utility of CCR5 receptor antagonists, or any other leukotoxin inhibitor, lies in its potential to facilitate natural clearance of acute infection due to blockade of immune cell killing. Such therapeutics could provide the additional advantage of enhancing adaptive immunity against *S. aureus* due to maintenance of antigen-presenting cell viability.

Importantly, *S. aureus* encodes other immune cell-targeting leukotoxins in addition to LukED. These toxins include Panton–Valentine leukocidin, γ -hemolysins (HlgAB and HlgCB) and leukocidin AB/GH. These toxins are all known to influence pathogenesis in animal models of infection, presumably through their lytic activities on immune cells. Given

the clinical implications arising from the identification of CCR5 as the cellular receptor for LukED, it is of interest to determine the molecular mechanism by which these additional leukotoxins target immune cells. Such findings will permit the development of novel approaches towards blocking toxin activity and increasing the viability of immune cells involved in infection resolution. The presence of multiple immune cell-targeting toxins in the *S. aureus* genome highlights a critical point for consideration in therapeutic development: targeting a single toxin in the treatment of a pathogen such as *S. aureus* is unlikely to be a reasonable curative strategy. It is now clear that the development of effective *S. aureus* therapeutics will rely on targeting multiple pathogenic molecules. We believe that pan-leukotoxin targeting represents an early advance towards this type of multifaceted therapy.

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