



# Structural insights into recognition of chemokine receptors by *Staphylococcus aureus* leukotoxins

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**Abstract** *Staphylococcus aureus* (SA) leukocidin ED (LukED) belongs to a family of bicomponent pore forming toxins that play important roles in SA immune evasion and nutrient acquisition. LukED targets specific G protein-coupled chemokine receptors to lyse human erythrocytes (red blood cells) and leukocytes (white blood cells). The first recognition step of receptors is critical for specific cell targeting and lysis. The structural and molecular bases for this mechanism are not well understood but could constitute essential information to guide antibiotic development. Here, we characterized the interaction of LukE with chemokine receptors ACKR1, CCR2, and CCR5 using a combination of structural, pharmacological, and computational approaches. First, crystal structures of LukE in complex with a small molecule mimicking sulfotyrosine side chain (p-cresyl sulfate) and with peptides containing sulfotyrosines issued from receptor sequences revealed the location of receptor sulfotyrosine binding sites in the toxins. Then, by combining previous and novel experimental data with protein docking, classical and accelerated weight histogram (AWH) molecular dynamics we propose models of the ACKR1-LukE and CCR5-LukE complexes. This work provides novel insights into chemokine receptor recognition by leukotoxins and suggests that the conserved sulfotyrosine binding pocket could be a target of choice for future drug development.

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**Competing interest:** The authors declare that no competing interests exist.

**Funding:** See page 27

**Received:** 27 July 2021  
**Preprinted:** 06 August 2021  
**Accepted:** 19 March 2022  
**Published:** 21 March 2022

**Reviewing Editor:** Aaron Frank, University of Michigan, United States

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## Editor's evaluation

In this report, the authors employed a wide array of biophysical tools and techniques to study the interaction of LukE toxin with chemokine receptors. Although follow-up studies will be required to substantiate all of the conclusions drawn by the authors, the paper will be of general interest as it provides insights into the molecular recognition mechanism of an important toxin interacting with cellular receptors.

## Introduction

*Staphylococcus aureus* (SA) is a major opportunistic human pathogen that causes a wide range of clinical manifestations (Tong et al., 2015), and poses growing health concern due to the emergence of multidrug resistant strains. Pathogenic SA strains produce a number of wall-associated or secreted virulence factors that promote growth, nutrient acquisition and evasion of the host immune system (DeLeo et al., 2009; Oliveira et al., 2018). Among this arsenal of virulence factors, the bicomponent