JEMTAC
Journal of Emergency Medicine Trauma & Acute Care
A PEER REVIEWED JOURNAL

OPEN ACCESS

Qatar Health 2022 Conference

Staphylococcus aureus histone deacteylase-like enzyme is a potential target for adjuvant antibiotic discovery

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ABSTRACT

Background: The rise in antibiotic resistance requires prompt action to reduce the burden of untreatable bacterial diseases[1]. *Staphylococcus aureus* is a human commensal and opportunistic pathogen that causes a broad range of diseases, from mild skin infections to infective endocarditis. The World Health Organization has placed *S. aureus* on the high-priority pathogen list due to its multidrug-resisting nature[2]. The study aims to identify molecular targets for antibiotic adjuvants to restore antibiotic activity.

Methods: Extensive blast search and computational analysis were employed to search published *S. aureus* genomes. The effect of suggested adjuvants was tested on sensitive and resistant *S. aureus* strains in-vitro. Bacteria were incubated in the presence of either an HDAC inhibitor (TSA) or an antibiotic (Cefixime), or a combination of both.

Results: A gene that encodes a histone deacetylase-like enzyme (SA-HDAC) and shares high 3D-homology to human HDAC2 and HDAC8 was identified[3]. Using computational modeling, it was found that the SA-HDAC protein has an active catalytic pocket containing the highly conserved zinc-binding constellation, suggesting an HDAC-like activity. I-TASSER analysis revealed that HDAC inhibitors such as TSA, CRI, LLX, NHB, and B3N can bind to the catalytic core. From the growth curves generated using the in-vitro study, it was observed that while Cefixime alone had no effect, TSA had an inhibitory effect, and the combination showed an additive effect on both strains. Further, the effect was more evident in the sensitive strain as compared to MRSA. An extensive bioinformatics blast search showed that this gene is absent in most gut microbiota species but found in many pathogens that carry and spread multidrug resistance in healthcare settings as well as in community-acquired infections.

Conclusion: SA-HDAC enzyme, which is absent in most gut microbiota, is a highly druggable target that can be utilized for novel adjuvant antibiotic discovery.

Keywords: Antimicrobial resistance, *Staphylococcus aureus*, Histone deacetylase, Trichostatin A, Adjuvant

http://dx.doi.org/10.5339/jemtac.2022.qhc.37

Submitted: 27 July 2021
Accepted: 18 August 2021
Publication date: 15 January 2022

QSCIENCE
HAMAD BIN KHALIFA UNIVERSITY PRESS

Cite this article as: Chowdhury SH, Zughaier SM. *Staphylococcus aureus* histone deacteylase-like enzyme is a potential target for adjuvant antibiotic discovery, *Journal of Emergency Medicine, Trauma & Acute Care* 2022:37 http://dx.doi.org/10.5339/jemtac.2022.qhc.37

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