

Pathway for Heme Uptake from Human Methemoglobin by the Iron-Regulated Surface Determinants System of Staphylococcus aureus

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Background and Objective: Heme is a preferred source of essential iron for pathogen *Staphylococcus aureus*. The *S. aureus* heme acquisition system consists of the surface proteins LsdA, LsdB, and LsdC and transporter LsdDEF. This study aims at establishing how this system takes up heme from methemoglobin (metHb).

Methods: Hemin transfer between the various couples of metHb and the Lsd proteins was investigated by spectroscopic and kinetic analyses. The efficiencies of hemin transfer from hemin-containing donors to hemin-free acceptors were examined, and the rates of the transfer reactions were compared to that of indirect loss of hemin from the relevant donor to H64Y/V68F apomyoglobin.

Results: The efficiencies, spectral changes, and kinetics of the transfer reactions demonstrate that: metHb directly transfers hemin to apo-LsdB, but not to apo-LsdA, apo-LsdC and apo-LsdE; holo-LsdB directly transfers hemin to apo-LsdA and apo-LsdC, but not to apo-LsdE; holo-LsdA directly transfers hemin to apo-LsdC; and apo-LsdE directly acquires hemin from holo-LsdC, but not from holo-LsdB and holo-LsdA (J Biol Chem 283:6668; in press).

Conclusion: These results provide direct evidence for a model in which LsdB acquires hemin from metHb and transfers it directly or through LsdA to LsdC. Hemin is then relayed to LsdE, the lipoprotein component of the LsdDEF transporter.

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