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Structural and Functional Diversity of Transient Heme Binding to Bacterial Proteins

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A B S T R A C T

Background: Heme is an important nutritional iron source for almost all bacteria. Elevated heme concentrations, in contrast, are toxic e.g. due to the generation of reactive oxygen species. The cellular heme concentration thus requires tight regulation. The observation of heme acting as an effector molecule in heme-uptake and -utilization processes is rather new and many of these processes are unknown or rarely understood on the molecular level.

Scope of review: We describe processes involving transient heme-protein interaction in bacteria and highlight the regulatory function of heme at key steps during heme uptake and utilization. We furthermore focus on essential structural aspects of heme binding to respective proteins.

Major conclusions: The structural and functional basis for heme-regulated processes in bacteria is diverse and ranges from increased degradation to extended half-life and from inhibition to activation of the respective heme-regulated protein. The large variety of effects is attributed to the versatile ability of heme to interact with proteins in different ways.

General significance: Knowledge of the molecular mechanism of transient heme-protein interaction is central to understand the heme-regulated processes in bacteria. The heme-binding proteins involved in these processes represent potential targets for the development of novel antibacterial drugs. New antibacterial strategies are urgently needed to combat antibiotic resistance.

Keywords: heme, heme uptake, heme utilization, heme-regulated proteins, bacteria

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1. Introduction

Iron protoporphyrin IX (PPIX) has a large variety of biological functions in almost all living organisms whereby the most abundant form is b-type heme (referred to as heme in the following text). Until recently, heme research was mainly connected to its role as a prosthetic group in a multitude of hemoproteins, providing these proteins with functionalities such as oxygen transport[1], gas sensing[2], catalytic activity and electron transfer[3]. In the last decades, the special function of heme as an effector molecule being involved in the regulation of cellular processes in different organisms[4] and its role as major iron source especially for pathogenic bacteria[5] has been disclosed. Heme and iron are critical nutrients for bacteria, which are vital for growth and survival as well as toxic if present in elevated concentrations[6]. Consequently, uptake and utilization of both, heme and iron, are highly regulated processes in bacteria, and malfunctions result in growth inhibition and cell death[6b, 7]. This provides an interesting starting point for the development of new classes of antibiotics[8]. The number of new antibiotics dramatically decreased since the 'golden era' in the 1960s[9]. Thus, new antibacterial agents are urgently needed due to the fatal antibiotic resistance development which, if not stopped, might set the health systems of the world back to the 'pre-