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Review

A battle for iron: host sequestration and *Staphylococcus aureus* acquisition

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Abstract

The use of iron as an enzymatic cofactor is pervasive in biological systems. Consequently most living organisms, including pathogenic bacteria, require iron to survive and replicate. To combat infection vertebrates have evolved sophisticated iron sequestration systems against which, pathogenic bacteria have concomitantly evolved equally elaborate iron acquisition mechanisms.

Keywords: Bacterial pathogenesis; *Staphylococcus aureus*; Isd system; Nutritional immunity; Staphylococcal iron acquisition

1. Introduction

Staphylococcus aureus is a Gram-positive coccoid bacterium that innocuously colonizes the anterior nares of approximately 30% of the human population [1]. However, upon breaching this initial site of colonization, *S. aureus* has the capacity to infect nearly every tissue in the human body. Consequently, *S. aureus* can cause a spectrum of ailments ranging from superficial wound infections to more severe diseases such as septicemia, toxic shock syndrome and endocarditis [2]. *S. aureus* is the most frequent cause of nosocomial infections in the United States, with the percentage of infections caused by methicillin resistant *S. aureus* (MRSA) growing precipitously [3]. The clinical challenge presented by MRSA is underscored by the fact that within the United States *S. aureus* is responsible for more deaths than HIV [4]. Furthermore, *S. aureus* has a remarkable capacity to resist currently available antimicrobials. Finally, in the last two decades there has been a dramatic increase in community acquired MRSA infections within populations that have not had identifiable exposure to health care institutions [2]. These facts highlight the need for the identification of new targets for the development of antimicrobials to treat this infectious threat [2].

A promising strategy to combat bacterial infections is to inhibit the procurement of nutrients that are necessary for growth. Iron is required by nearly all living organisms and *S. aureus* is no exception. The vertebrate host tightly regulates iron levels and sequesters this valuable nutrient intracellularly as a mechanism to prevent bacterial proliferation. Extracellular iron is rapidly removed by transferrin and lactoferrin, proteins with a high affinity for iron. Furthermore, the majority of iron within vertebrates is complexed to the porphyrin heme which is bound by hemoproteins. This process of limiting access to nutrient metal is known as nutritional immunity [5]. *S. aureus* responds to the iron-restricted environment of the host through the coordinated up-regulation of iron acquisition systems and other virulence factors. This review addresses the dynamic relationship between host-mediated iron sequestration and staphylococcal iron acquisition strategies.

2. Nutritional immunity

Nutritional immunity is a complex process requiring the synchronization of multiple enzymes involved in host iron regulation. Iron is insoluble at physiologic pH found within vertebrate tissues and any free iron is quickly removed by

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high-affinity iron binding proteins. Within the serum, free iron is bound by transferrin with an association constant of approximately 10^{36} [5]. In addition to binding free iron, transferrin functions as an iron transport protein, transferring iron to peripheral tissues through receptor-mediated endocytosis of transferrin receptor 1 (TfR1) upon complexation with holo-transferrin (Fig. 1) [6]. Iron levels are also limited in lymph and mucosal secretions through lactoferrin, which quickly binds all free iron. Additionally, lactoferrin is a major component within phagocytes, ensuring that engulfed pathogens have limited access to intracellular iron. In healthy individuals both lactoferrin and transferrin are only 30–40% saturated and consequently are poised to bind free iron [5].

The overwhelming majority of iron within humans is found in the form of heme; a tetrapyrrole ring with a coordinated iron center. Heme is often bound by hemoproteins, the most abundant of which is hemoglobin. To further prevent access to iron, hemoglobin is sequestered intracellularly within erythrocytes; greater than 90% of iron within the human body is located intracellularly making it inaccessible to extracellular pathogens unless mechanisms are employed to liberate these rich sources of nutrient iron. Although hemoglobin is the most abundant hemoprotein in the body, there are additional heme-binding proteins that can serve as sources of iron for invading bacteria. Haptoglobin is a tetrachain ($\alpha 2\beta 2$) glycoprotein that binds free hemoglobin following hemolysis as a means to prevent loss of iron through urinary excretion and subsequent kidney damage [7]. *S. aureus* binds haptoglobin–hemoglobin complexes *in vitro,* suggesting that this protein complex is exploited as a source of nutrient iron [8]. Myoglobin is an

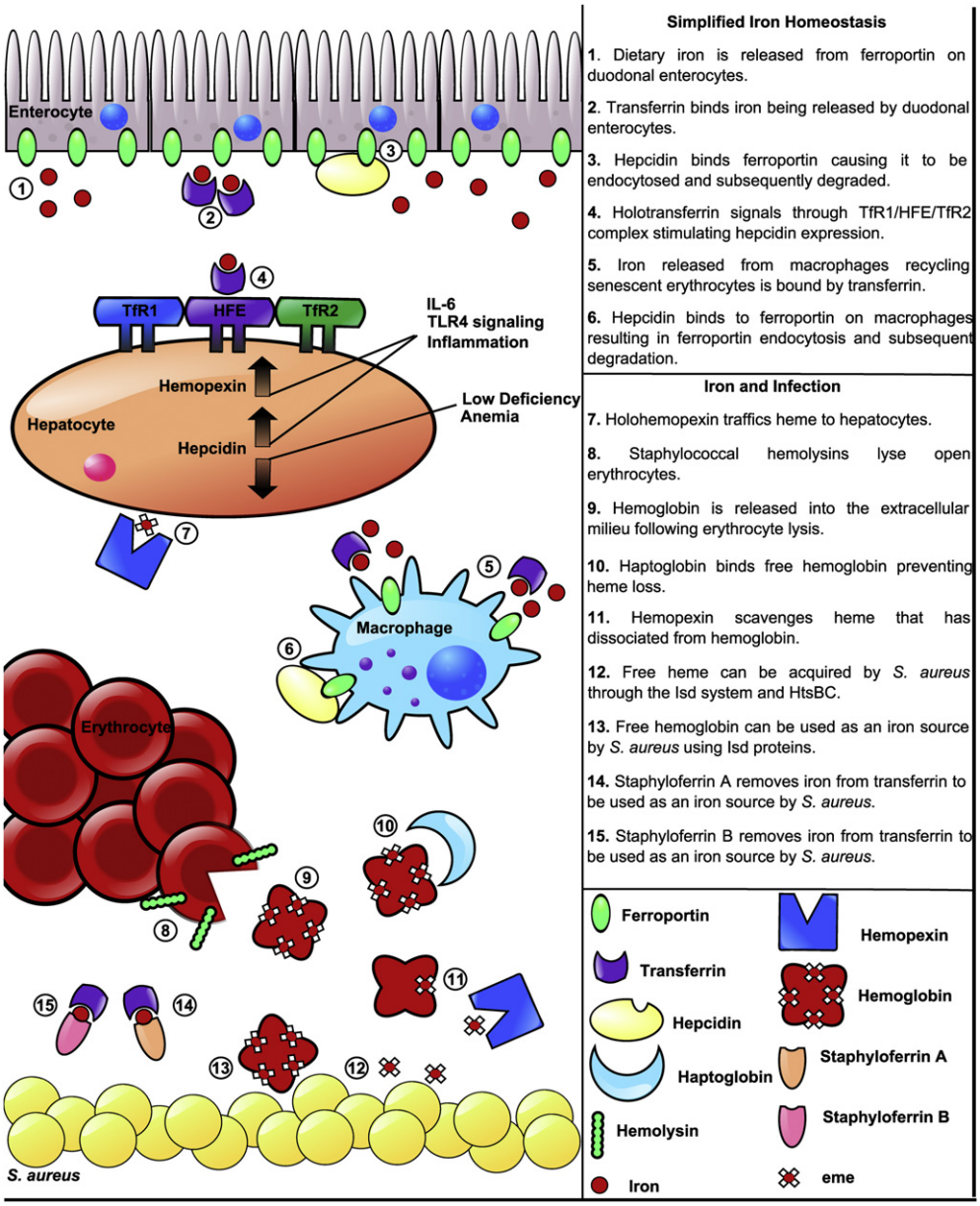

Fig. 1. Iron homeostasis in health and disease.