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Review Article

Siderophore-mediated iron acquisition and modulation of host-bacterial interactions

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ABSTRACT

Iron is an essential micronutrient for most life forms including the majority of resident bacteria of the microbiota and their mammalian hosts. Bacteria have evolved numerous mechanisms to competitively acquire iron within host environments, such as the secretion of small molecules known as siderophores that can solubilize iron for bacterial use. However, siderophore biosynthesis and acquisition is not a capability equally harbored by all resident bacteria. Moreover, the structural diversity of siderophores creates variability in the susceptibility to host mechanisms that serve to counteract siderophore-mediated iron acquisition and limit bacterial growth. As a result, the differential capabilities to acquire iron among members of a complex microbial community carry important implications for the growth and function of resident bacteria. Siderophores can also directly influence host function by modulating cellular iron homeostasis, further providing a mechanism by which resident bacteria may influence their local environment at the host-microbial interface. This review will explore the putative mechanisms by which siderophore production by resident bacteria in the intestines may influence microbial community dynamics and host-bacterial interactions with important implications for pathogen- and microbiota-driven diseases including infection, inflammatory bowel diseases and colorectal cancer.

1. Introduction

The gastrointestinal (GI) tract is home to a collection of microbial communities collectively known as the intestinal microbiota. In fact, nearly all other healthy body sites that are colonized with distinct microbial communities comprise a specific host-associated microbiota [1,2]. At birth, the GI tract becomes rapidly colonized with a community of microbes that over the first several years of life, increases in complexity and stabilizes into a mature state [3,4]. The bacterial phyla Firmicutes and Bacteroidetes comprise the majority of the normal adult enteric microbiota, with Actinobacteria, Proteobacteria and Verrucomicrobia present in lesser abundances [5]. However, the composition of the microbiota is not static and undergoes temporal variations as a result of environmental factors including but not limited to dietary changes, exposure to pathogens and xenobiotics, inflammation and overall health status of the host [6–11]. Moreover, variations in the spatial distribution of nutrient availability and host-derived factors results in compositionally and metabolically distinct bacterial communities residing within the lumen, at the mucosa, and longitudinally along the GI tract [12,5,13,14].

The intestinal microbiota, in symbiosis with the host, is integral to numerous host processes including immune system development and nutrient metabolism [15–21]. The intestinal microbiota is physically separated from the underlying mucosal immune system by a single layer of epithelial cells, a thick layer of mucus and host secretions including antimicrobial peptides and soluble immunoglobulin A (IgA) antibodies that collectively make up the intestinal barrier. The mucosal immune system is tasked with remaining tolerant of resident microbes while responding to pathogens and other microbes that breach the intestinal barrier in order to limit uncontrolled inflammatory responses and systemic dissemination [22]. However, resident bacteria do not play a passive role in maintaining this symbiotic relationship. Depletion of specific bacterial groups through the use of antibiotics and colonization of germ free mice with a single bacterial strain or defined community (i.e. gnotobiotic mice) have revealed that select members of the intestinal microbiota can modulate specific host responses within the intestines [23]. Some resident bacteria induce tolerogenic and anti-inflammatory immune responses and enhance barrier function [24–28], while others favor the establishment of a more proinflammatory microenvironment [25,29,30]. Blooms of resi-

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dent bacteria with greater proinflammatory potential and/or their mislocalization to mucosal sites enhance the opportunity for inappropriate microbial stimulation of the mucosal immune system, which can ultimately compromise the symbiotic relationship between the microbiota and the host. These unfavorable compositional and functional changes to the microbiota, collectively known as dysbiosis, have been associated with acute inflammatory insults such as enteric infection as well as chronic diseases including inflammatory bowel diseases (IBD) and colorectal cancer [31–35].

Nearly all bacteria and their mammalian hosts compete for iron, an essential micronutrient. Iron serves as a cofactor for numerous cellular proteins involved in diverse processes including DNA synthesis and repair, cellular respiration, biodegradation and biosynthetic pathways and transcriptional regulation [36]. However, given the propensity for free iron to participate in Fenton chemistry and generate toxic reactive oxygen species (ROS), the abundance of free iron must be tightly regulated. Under most physiological conditions (i.e. oxygenated and neutral pH), non-heme iron predominates in its ferric form and exhibits low bioavailability. To overcome this, both host and microbe encode enzymes that reduce ferric iron into its more soluble ferrous form and secrete proteins or small compounds termed siderophores that sequester extracellular ferric iron for cellular use. The necessity of iron for growth of most pathogenic invaders and resident bacteria sets the stage for an evolutionary battle for iron between host and microbe at the mucosal interface. Indeed, as a key component of the host innate immune response, bacterial iron availability is limited by mucosal secretion of host iron binding proteins to prevent systemic dissemination of pathogens and ensure luminal compartmentalization of endogenous bacteria to maintain symbiosis. However, some bacteria taxa – both pathogen and resident – have acquired mechanisms of iron acquisition that overcome attempts by the host to limit iron availability, a competitive advantage that can impact interbacterial interactions within the microbiota and interkingdom interactions between resident bacteria and their hosts [37–40]. This review will largely focus on how siderophore-mediated bacterial iron acquisition can shape bacterial community dynamics and host-microbial interactions within the intestinal environment.

2. Siderophore-mediated iron acquisition

Bacterial iron homeostasis is tightly regulated to enable the acquisition of sufficient iron while also limiting toxicity from iron-mediated production of reactive oxygen species. Accordingly, the expression of iron acquisition systems is restricted to environments where iron stores are depleted. Changes in intracellular iron concentrations are sensed by the ferric uptake regulator (Fur), the master transcription factor of iron homeostasis in a wide range of bacterial taxa [41,42,39]. When intracellular iron is replete, the Fur-Fe2+ complex inhibits transcription of genes involved in iron acquisition, thus preventing excess iron import into the cell [43,44]. Under iron limiting conditions, apo-Fur predominates in the cell, resulting in the de-repression of iron acquisition genes and consequent iron transport into the cell.

Mechanisms of bacterial iron acquisition include siderophore-mediated transport, direct import through divalent metal transporters or direct piracy from iron-bound host proteins [41,45,37,39]. Siderophores are low molecular weight compounds with high affinity for ferric iron, and are synthesized and secreted by bacteria in order to scavenge iron when availability is limited. In Gram-negative bacteria, siderophore-bound iron is transported through cognate outer membrane receptors that require energy transduction by the TonB-ExbB-ExbD protein complex [41,46]. In the periplasm, a chaperone protein binds the iron-chelate and delivers the complex to cognate ABC permeases on the inner membrane. Gram-positive bacteria utilize a similar mechanism of siderophore transport through ATP-binding cassette (ABC) transporters localized at the cytoplasmic membrane [47]. Once within the cytoplasm, iron is liberated from the siderophore by one of two mechanisms [37]. The more common approach occurs by reduction of ferric iron to its ferrous form by non-specific ferrisiderophore reductases, often flavin reductases that also serve other cellular functions. The decreased affinity for ferrous iron is then thought to enable the spontaneous release of iron from the siderophore. The second mechanism depends on specific enzymatic hydrolysis of the siderophore, which serves to weaken its interactions with iron and enable its liberation. In both Gram-negative and -positive organisms, ferrous iron is directly transported through cytoplasmic membrane permeases or ABC transporters [48,49]. Some bacterial pathogens are also capable of utilizing host sources of iron by expressing outer membrane receptors that directly bind to host iron binding proteins such as transferrin [45].

Siderophores are a structurally diverse group of compounds that impart distinct functional attributes to bacteria. Siderophores can be categorized into three main structural families – carboxylate, catecholate, and hydroxamate – named accordingly to the functional groups that confer their binding affinity and selectivity for ferric iron [40,37,50]. Some common siderophores produced by enteric bacteria are listed in Table 1. There are also many siderophores such as yersiniabactin and aerobactin that either incorporate more than one of these functional groups within their structures or contain additional functional groups that interact with the ferric iron ion. Carboxylate siderophores such as staphyloferrin A exhibit a greater affinity for ferric iron at acidic pH ranges and therefore likely contribute to enhanced fitness within more acidic environments. In contrast, under physiologic conditions, catecholate siderophores such as enterobactin and salmochelin exhibit higher affinity for ferric iron relative to carboxylate or hydroxamate siderophores. Indeed, enterobactin exhibits the highest known affinity for ferric iron and outcompetes the host iron binding protein transferrin for iron, thus enabling bacteria to thrive within transferrin-rich environments [40,51]. Given the chemical diversity of siderophores, harboring distinct siderophore systems likely imparts unique fitness advantages to bacteria within a varied range of environments. Indeed, encoding numerous siderophore systems is associated with enhanced fitness for both pathogenic and resident bacteria within the intestines [52] and at many extraintestinal sites [53–55,51].

3. Bacterial iron availability in the GI tract

Within the GI tract, a major source of iron for resident bacteria comes from the diet. About 5–15% of non-heme iron is absorbed in the duodenum [56], leaving the remaining unabsorbed iron to pass through the intestines. Supporting the role of diet as a modulator of colonic iron concentrations, consumption of an iron-fortified diet or oral iron supplements increases total non-heme iron concentrations in

Table 1
Common siderophores produced by enteric bacteria [37,40,50].

Bacterial taxa	Siderophores produced	Structure
Enterobacteriaceae (including *E. coli*, *S. enterica*, *Shigella spp.*, *Yersinia spp.*, *Klebsiella spp.*)	Enterobactin	Catecholate
	Salmochelin	Catecholate (glycosylated enterobactin)
	Aerobactin	Mixed (carboxylate-hydroxamate)
	Yersiniabactin	Mixed (phenolate)
Pseudomonas spp.	Pyochelin	Mixed (phenolate)
	Pyoverdin	Mixed
Staphylococcus spp.	Staphyloferrin A	Carboxylate
Bacillus spp.	Bacillibactin	Catecholate
	Petrobactin	Mixed (carboxylate-catecholate)
Vibrio spp.	Vibriobactin	Catecholate

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