Siderophores – potential candidate in the therapy of neonatal meningitis

The mortality and morbidity associated with neonatal meningitis remain significant in spite of advances in antimicrobial chemotherapy (Kim, 2003). *Escherichia coli* k1 is a successful pathogen capable of invading the brain despite the protective effect of physiological barriers between the bloodstream and the central nervous system. Inadequate knowledge regarding the pathophysiology of this organism along with poor drug delivery to the brain has resulted in a lack of success following therapy of this infection. Investigations regarding neonatal meningitis have focused on the determination of resistance to antibiotics, but alternate therapies exploiting the modulation of the environment for invading bacteria have not been explored (Nigrovic et al., 2004; Shah et al., 2004; Kumar, 2004).

Iron supply for many microbes plays a decisive role in the infection process. Acquiring iron from the environment has a significant effect on the establishment of infection in the host, and microbial pathogens have evolved different mechanisms to overcome iron restriction. The role of iron chelation in virulence has been evaluated for microbial organisms (Dale et al., 2004). Iron facilitates the progression of high-level *E. coli* bacteremia to meningitis. Indeed, it has been shown elsewhere that the ferric-siderophore uptake system is a critical factor in the progression of high-level pathogenicity of *E. coli*. Acquiring iron from the environment has a decisive role in the infection process. Iron supply for many microbes plays a decisive role in the infection process.

Iron restriction for bacterial pathogens is a widely used phenomenon in host defence against infection. Removal of iron as a therapeutic approach has been investigated *in vitro* for several infections (Gomes et al., 1999; Mabeza et al., 1999). Removal of iron has been shown to improve the clinical outcome in a number of infectious diseases (Lounis et al., 2001; Schaible et al., 2002). Genetic and biochemical studies have allowed substantial progress in understanding the molecular mechanisms of iron-scavenging in virulence of pathogenic bacteria. The microbicidal activity of iron chelation is thought to be either due to iron chelators reducing bacterial growth through their ability to withhold iron from the bacterial pathogen or due to the formation of toxic complexes (Mabeza et al., 1999).

Chelation of iron in order to inhibit growth of invading bacteria could be developed into a therapy against neonatal infection. Siderophores generate stress by acquisition of iron from the environment and inhibit the growth of invading bacteria. We have previously shown that a plant-based siderophore is capable of stopping the growth of *Mycobacterium tuberculosis* (Rajiv et al., 2001). Negre et al. (2004) showed that the *iroN* gene plays a key role in the virulence of *E. coli* and an *iroN* mutant lacking siderophore receptors differs from the wild-type strain in its ability to cause bacteremia, suggesting that iron acquisition by a siderophore is the most likely mechanism of the *iroN*-associated virulence. Thus, stress generated by the acquisition of iron by a siderophore will reduce invading *E. coli* burden. The role of different siderophores in reducing the *E. coli* burden, and therefore their role in therapy, remains to be determined and justifies further studies in this regard. An understanding of this process could result in a novel therapeutic strategy for management of neonatal meningitis.

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