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COLLEGE OF PHYSICAL AND APPLIED SCIENCES

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PRIFYSGOL BANGOR UNIVERSITY

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"Transferrin: the Battle between Man and Microbe"

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Abstract: Iron is an essential trace element for almost all organisms as it has a structural or functional role in a number of proteins and enzymes, including those involved in oxygen transport and storage, electron transport and DNA synthesis. The redox properties of iron play an important part in its role in biological systems. However, the ferric [Fe(III)] form is characterised by a low solubility at neutral pH, whereas the ferrous [Fe(II)] form is able to catalyse the Fenton reaction and generate potentially harmful hydroxyl radicals and related species.

Iron is highly conserved in Man and daily iron losses are normally between 0.5 and 2 mg via non-specific processes. These losses are compensated for by absorption of an equivalent amount of iron from the diet. However, the process of iron absorption is relatively inefficient and the amount of iron absorbed is dependent on the nature of the food ingested. The precise regulation of cellular iron uptake and storage is very important if individuals are to avoid conditions of iron deficiency, as a result of a failure to absorb sufficient dietary iron, or iron overload, as a result of increased absorption of dietary iron or repeated blood transfusions, as in the case of patients with β-thalassaemia.

Although iron is an essential element for most bacteria, the "free" concentration of ferric iron in extracellular fluids such as plasma has been estimated to be as low as 10^{-18} M. Bacteria have therefore evolved ways to obtain their essential iron, for example by synthesising high-affinity iron chelators (siderophores) or by expressing surface receptors capable of scavenging iron from the

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mammalian host's iron-containing proteins such as transferrin and lactoferrin. Under iron-limiting conditions *Neisseria meningitidis*, the causative agent of meningococcal meningitis and septicaemia, expresses transferrin-and lactoferrin-binding proteins (Tbps and Tbps) in its outer membrane. These receptors, which display an absolute specificity for human transferrin and human lactoferrin, respectively, comprise an integral membrane protein (TbpA and LbpA) and a surface-exposed lipoprotein (TbpB and LbpB). Although a vaccine is now available to prevent the serogroup C meningococcal disease, no vaccine is available to prevent the serogroup B disease, the most prevalent in the Western world. However, as TbpA is highly conserved amongst meningococcal strains, is surface-exposed and vitally important for the pathogenicity of the organism, it is under consideration for inclusion in a vaccine effective against all serogroups.

An understanding of both the nature of the interaction of transferrins with the meningococcal receptor complexes and the mechanism whereby the pathogen acquires its ligand-bound iron is essential to the development of rational strategies against meningococcal meningitis.

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