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Hypothesis: iron chelation plays a vital role in neutrophilic inflammation.

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Neoplasms - etiology - metabolism

Neutrophils - drug effects - enzymology - pathology

Oxidation-Reduction

Phagocytes - cytology - drug effects - metabolism

Abstract: Neutrophil influx into tissues occurs in many diverse diseases and can be associated with both beneficial and injurious effects. We hypothesize that the stimulus for certain neutrophilic inflammatory responses can be reduced to a series of competing reactions for iron, with either a labile or reactive coordination site available, between host chelators and chelators not indigenous to that specific living system. The iron focuses the transport of host phagocytic cells through a metal catalyzed generation of oxidant sensitive mediators including cytokines and eicosanoids. Many of these products are chemotactic for neutrophils. We also postulate that the iron increases the activity of the phagocyte associated NADPH oxidoreductase in the neutrophil. The function of this enzyme is likely to be the generation of superoxide in the host's attempt to chemically reduce and dislodge the iron from its chelate complex. After the reoxidation of Fe2+ in an aerobic environment, Fe3+ will be coordinated by host lactoferrin released by the neutrophil. When complexed by this glycoprotein, the metal does not readily undergo oxidation/reduction and is safely transported to the macrophages of the reticuloendothelial system where it is stored in ferritin. Finally, we propose that the neutrophil will attempt to destroy the chelator not indigenous to the host by releasing granular contents other than lactoferrin. Inability to eliminate the chelator allows this sequence to repeat itself, which can lead to tissue injury. Such persistence of a metal chelate in the host may be associated with biomineralization, fibrosis, and cancer.

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