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Review

The role of HIF in immunity and inflammation

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ABSTRACT

Uncontrolled or non-resolving inflammation underpins a range of disease states including rheumatoid arthritis, inflammatory bowel disease and atherosclerosis. Hypoxia is a prominent feature of chronically inflamed tissues. This is due to elevated oxygen consumption by highly metabolically active inflamed resident cells and activated infiltrating immunocytes, as well as diminished oxygen supply due to vascular dysfunction. Tissue hypoxia can have a significant impact upon inflammatory signaling pathways in immune and non-immune cells and this can impact upon disease progression. In this review, we will discuss the relationship between tissue hypoxia and inflammation and identify how hypoxia-sensitive signaling pathways are potential therapeutic targets in chronic inflammatory disease.

Contents

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1. Hypoxia in inflammation

Metazoans have evolved a highly efficient bio-energetic strategy, which involves the oxidative metabolism of carbohydrates and fatty acids to produce biochemical energy equivalents in the form of adenosine triphosphate (ATP). This process occurs in mitochondria in the presence of sufficient levels of molecular oxygen (O_2). Under normal circumstances, the majority of oxygen available in a tissue is consumed during oxidative metabolism; however, a reserve of non-mitochondrial oxygen is also normally available (Hagen et al., 2003; Taylor, 2008). This non-mitochondrial oxygen acts both as an oxygen reserve and a sensed signal, which provides information to a cell that the tissue is receiving sufficient oxygen to meet metabolic requirements. Tissue hypoxia occurs when this state of oxygen homeostasis is disrupted and a condition where oxygen demand exceeds supply ensues. Under hypoxic-conditions, the reserve of non-mitochondrial oxygen is consumed to maximize ATP production and adaptive pathways are activated. Tissue hypoxia may occur as a result of diminished oxygen supply or increased oxygen demand.

It has recently become clear that tissue hypoxia is a prominent feature in a range of disorders where inflammation plays a prominent causative role including atherosclerosis, arthritis, inflammatory bowel disease (IBD), infection, obesity and cancer (Eltzschig and Carmeliet, 2011). Taking the intestinal mucosa as an example, a number of studies have now demonstrated that this tissue becomes profoundly hypoxic under conditions of inflammation (Colgan and Taylor, 2010; Taylor and Colgan, 2007). In the normal physiologic state, the intestinal mucosa has a steep oxygen gradient from crypt to villus tip (Zheng et al., 2015). This is likely a consequence of a countercurrent exchange (Hallback et al., 1978) of oxygen flow in the villus, and the fact that the intestinal epithelium is in direct contact with the anoxic lumen of the gut. Under conditions where the mucosa becomes inflamed, such as in inflammatory bowel disease (IBD), a profound degree of hypoxia occurs (e.g. surface oxygen tension measured in rabbits ranged from 36 ± 5 torr in control animals, 11 ± 5 torr in mild colitis and 4 ± 1 torr in severe colitis (Hauser et al., 1988)). The reasons for the occurrence of hypoxia at sites of inflammation are manifold and will be outlined below (Fig. 1).

A key reason for the occurrence of tissue hypoxia in inflammation is the increased demand for oxygen, which occurs when a tissue becomes inflamed. Following an

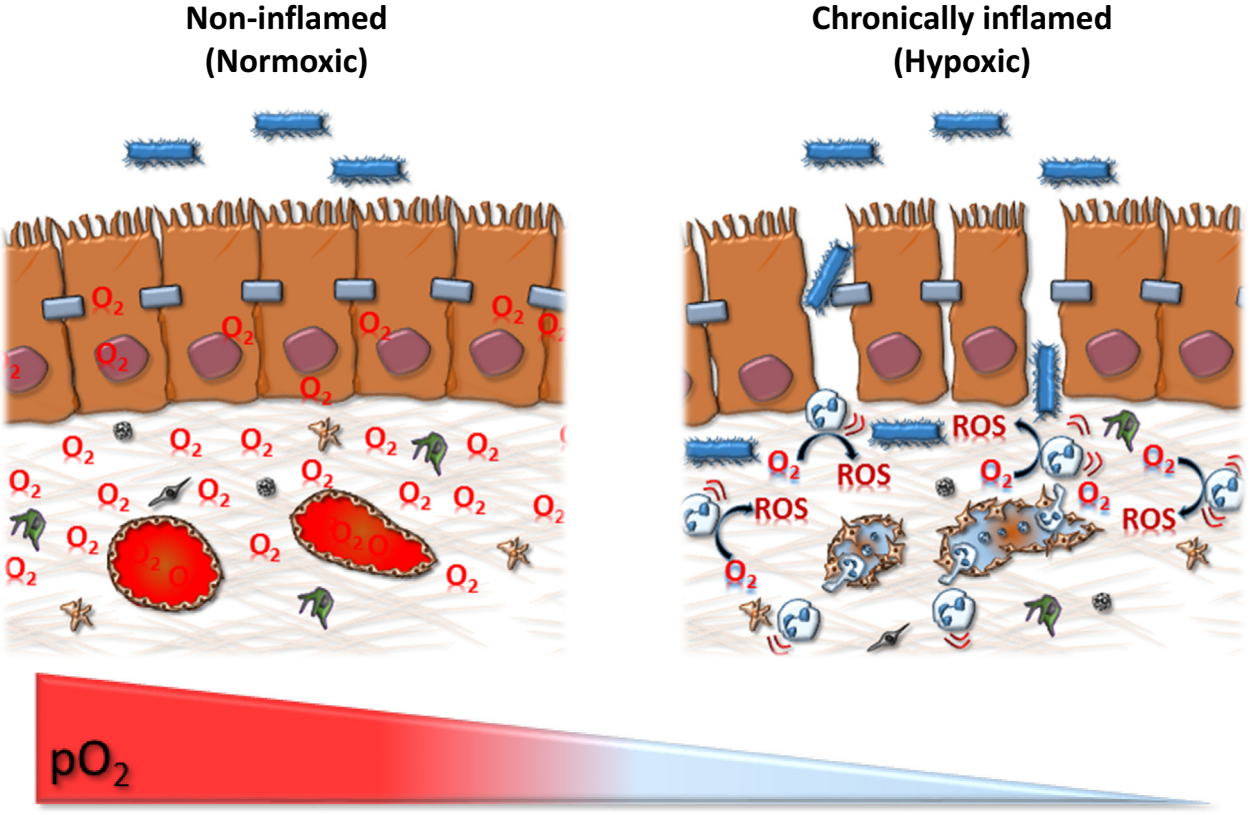

Fig. 1. Causes of tissue hypoxia in the inflamed intestine. In the healthy state (left hand side), the intestinal epithelium serves as an effective barrier separating the intestinal microbiota from the mucosal immune system. Under such conditions, the tissue receives sufficient oxygen supply through the mucosal microvasculature. In the inflamed intestine (right hand side), an increase in intestinal permeability leads to transmigration of intestinal microbiota and luminal antigens to the submucosal compartment resulting in the initiation of mucosal inflammation. The infiltration of activated neutrophils, which consume oxygen during the oxidative burst, and the induction of microvascular dysfunction leading to a decrease in oxygen supply combine to render the inflamed mucosa hypoxic.