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Review

Hypoxia modulates innate immune factors: A review

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ABSTRACT

Hypoxia is an important factor for transcriptional regulation of cell metabolism and the adaptation to cellular stress. It modulates the function of phagocytic cells by stimulating surface receptors such as scavenger receptors, toll like receptors and their downstream signaling cascades. In response to hypoxia, innate immune modifiers are upregulated through pathways involving the key immune response master regulator nuclear factor-κB leading to the modulation of inflammatory cytokines. In this review, we highlighted the effects of hypoxia on different innate immune factors and consequences thereof.

Contents

1. Introduction

A wealth of emerging information indicates that hypoxia deeply affects the regulatory pathways of innate immune defense. In *in vivo* system hypoxia is thought to occur in any tissue where alteration in perfusion causes a significant reduction in tissue oxygen levels relative to those that exist normally. Functionally, hypoxia occurs *in vivo* when oxygen demand exceeds oxygen supply. In healthy tissues the oxygen tension is generally 20–70 mm Hg (2.5–9% Oxygen), whereas markedly lower level (<1% oxygen) has been described in wound and necrotic tissue sites [1,2]. Within tissues, the partial pressure of oxygen (pO_2) decreases depending on the distance of cells from the closest oxygen supplying blood vessel. The hypoxic response is crucial for tissue homeostasis and cell survival in low oxygen environments, and is essential for the normal function of innate immune cells in oxygen-deprived tissues. The low partial pressure of oxygen at high altitudes affects the functioning of the immune system [3]. Cells of the innate immune system are usually the first to arrive at a diseased or wounded site, and are therefore able to withstand the presence of low pO_2. Neutrophils are pre-adapted because they contain few mitochondria and gain most of their energy from anaerobic glycolysis. Macrophages usually arrive shortly after neutrophils, and adapt their metabolic activity in a number of ways when exposed to hypoxia [2]. It has been established that innate immunity and the hypoxic response are linked at the molecular level, but the exact nature of this link was not previously known. The present review emphasizes the effect of hypoxia on innate immune factors and their consequences.

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2. Effect of hypoxia on TLR4 expression

Toll-like receptors (TLRs) are germ line-encoded innate immune receptors that recognize invading micro-organisms and induce immune and inflammatory responses [4]. Deregulation of TLRs is known to be closely linked to various immune disorders and inflammatory diseases. In mammals, TLRs mediate host immune responses by inducing the secretion of several pro-inflammatory cytokines and co-stimulatory cell-surface molecules through the activation of transcription factors such as nuclear factor-κB (NF-κB) and AP-1. Pathogen associated molecular patterns (PAMPs) or membrane-bound heat shock proteins (HSPs) or extracellular HSPs upon active secretion by stressed cells may also serve as an immunostimulatory signal through TLRs, which, in turn, leads to the expression of various effector molecules [5]. Cells at sites of inflammation are exposed to hypoxic stress, which further aggravates inflammatory processes. Kim et al. [6] have investigated the role of hypoxia-inducible factor 1 (HIF-1) in the regulation of TLR4 expression. Knockdown of HIF-1α expression by small interfering RNA inhibited hypoxia-induced TLR4 expression in macrophages, while over-expression of HIF-1α, potentiated TLR4 expression. Furthermore, Up-regulation of TLR4 expression by hypoxic stress enhanced the response of macrophages to lipopolysaccharide, resulting in increased expression of cyclooxygenase-2, interleukin-6, regulated on activation normal T cell expressed and secreted (RANTES), and interferon-inducible protein-10. These results demonstrated that TLR4 expression in macrophages is up-regulated *via* HIF-1 in response to hypoxic stress, suggesting that hypoxic stress at sites of inflammation enhances susceptibility to subsequent infection and inflammatory signals by up-regulating TLR4. In contrast Ishida et al. [7] reported that hypoxia decreases TLR4 expression in endothelial cells and this change is mediated by mitochondrial ROS leading to attenuation of AP-1 transcriptional activity. Hara et al. [8] also investigated whether hypoxia is involved in the activation of the TLR4 signaling systems in human corneal epithelial cells (HCECs). To accomplish this, experiments were conducted on a simian virus 40 immortalized human corneal epithelial cell line (SV40-HCEC) under normoxic and hypoxic conditions. The authors also examined the expression of the mRNA of TLR4 in the HCECs of hydrogel soft contact lens (SCL) wearers; the expression of TLR4 was decreased in the HCECs of SCL wearers and SV40-HCECs under hypoxic conditions. In addition, hypoxia decreased the LPS-induced expression of IL-6 and IL-8 as well as the activation of NFκB in SV40-HCECs. These results indicate that the contact lens induced hypoxia may increase the susceptibility to bacterial infections such as *Pseudomonas aeruginosa* by altering the TLR4 signaling pathways. Based on the contrast findings of above literatures we conclude that whether hypoxia upregulates or downregulates the TLR4 expression is still debatable and needs to be investigated.

3. Effect of hypoxia on phagocytosis

Phagocytosis is an important innate immune mechanism. Immune cells such as macrophages and neutrophils conduct most of the phagocytosis. Phagocytosis is the process that leads to ingestion of the particles. It involves both attachment to receptors and subsequent engulfment. After engulfment, phagosomes are formed that surround the microbe followed by fusion of secretory granules with phagosomes to form phagolysosomes. Killing and digestion of the microorganisms take place within these phagolysosomes [10]. Phagocytosis is important for bacterial clearance and thereby relevant to the systemic inflammatory diseases which are associated with the development of hypoxia [10]. Evidence in support of a possible role for hypoxia in the modulation of phagocytosis includes the finding that hypoxia itself is known to cause the activation of intracellular signaling pathways, it upregulates p38 MAPK which helps in particle internalization. Fritzenwanger et al. [9] performed the experiments on healthy volunteers exposed to hypoxia in a specialized hypoxia chamber, and analyzed the phagocytic capacity of neutrophils and monocytes; they reported that short term systemic hypoxia increased phagocytosis of neutrophils without influencing phagocytosis of monocytes.

4. Effect of hypoxia on nitric oxide (NO) production

Nitric oxide (NO) is a molecule both omnipotent and omnipresent in human biology. It is an important mediator of homeostatic processes and host immunity. Its discovery is not only an important addition to our understanding of biology but also in foundation for development of new approaches for management and treatment of various diseases. There are many reports about the effects of hypoxia on NO production.

Archer et al. [11] examined the effects of graded hypoxia on several steps in the iNOS pathway in lipopolysaccharide (LPS)-stimulated rat glomerular mesangial cells: induction of iNOS mRNA, NO synthesis, NO oxidation to nitrite (NO_2^-) and nitrate (NO_3^-), and accumulation of cGMP. They concluded that although hypoxia can alter the partitioning and decomposition of NO, the induction of iNOS mRNA and the activity of its enzyme products are resistant to hypoxia. In another study, Louis et al. [12] showed that arginase may also modulate NO production by macrophages *via* reduced availability of L-arginine. It has been found that while anoxia can cause stimulation in the metabolism of L-arginine, hypoxia up-regulates iNOS activity in murine ANA-1 cells as a single stimulus. Furthermore, Angele et al. [13] reported that regional hypoxia, associated with hemorrhage, is thought to induce a variety of alterations in immune cell function, including upregulation of macrophage-inducible nitric oxide synthase (iNOS) expression and activity. Lewis et al. [14] showed that the ability of hypoxically activated macrophages to make NO may in fact be decreased *in vivo* by reduced levels of L-arginine due to simultaneous arginase stimulation. Daniliuc et al. [15] reported that hypoxia regulates the high output macrophage iNOS and hence NO production. It was shown that hypoxia inhibits iNOS activity without interfering with the expression of protein. Grilli et al. [16] showed that hypoxia enhances NO formation in cardiomyocytes, in the lung and in pulmonary endothelial cells, whereas inhibition of NO production by hypoxia in pulmonary arteries, pulmonary endothelial cells and aortic endothelial cells was also reported. Daniliuc et al. [15] observed that hypoxia alone induced iNOS expression, and that the addition of LPS synergistically increased its levels. Vascular NO can also be increased under hypoxic conditions by nitrite reductase activities of several proteins including hemoglobin, myoglobin and xanthase oxidase [17–20]. Robinson et al. [21] reported that physiological and hypoxic O_2 tensions rapidly regulate NO production by stimulating macrophages.

The heterogeneity of the results may be due to differences in experimental protocol, from animals and tissues examined, or from the duration of hypoxia.

5. Effect of hypoxia on scavenger receptor

Macrophages are distributed in all peripheral tissues and play a critical role in the first line of the innate immune defenses against bacterial infection by phagocytosis of bacterial pathogens through the macrophage scavenger receptor 1 (MSR1). However, it is not clear how the expression of MSR1 in macrophages is regulated by low pO_2. Shirato et al. [22] investigated the effects of hypoxia and HIF-1α on MSR1 expression and its function in the macrophage cell line RAW264. Exposure to 1% O_2 significantly suppressed the expression of MSR1 mRNA, accompanied by a marked increase in levels of nuclear HIF-1α protein. They concluded that hypoxia transcriptionally suppresses MSR1 expression through HIF-1α.

6. Effect of hypoxia on inflammatory cytokine production

IL-1 and related family members IL-6, IL-8 and TNF-α are the prototypic cytokines associated with inflammatory responses, which are