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Unravelling the Role of HIF-1α in Sepsis

A recent review explores the crucial role of hypoxia-inducible factor-1α (HIF-1α) in the development and progression of sepsis.

Hypoxia-inducible factor (HIF) is a protein complex consisting of a constitutively expressed subunit β and an oxygen-dependent subunit α. HIF-1α is associated with acute hypoxia and regulates glycolytic genes, oxygen consumption, and reactive oxygen species production. It belongs to the bHLH-PAS family, facilitating dimer formation with HIF-1β and binding to hypoxia response elements (HRE) on target genes. HIF-1α contains transactivation domains (TAD) that stabilise the protein and prevent degradation.

HIF-2α functions predominantly in chronic hypoxia, regulating erythropoietin synthesis, iron metabolism, fatty acid synthesis and uptake, and influencing chronic inflammation, fibrosis, and tumorigenesis. HIF-3α also plays a role in the hypoxia response, competitively binding to transcriptional elements of target genes during hypoxia and negatively regulating gene expression associated with the HIF pathway.

In bacterial sepsis, elevated levels of HIF-1α are observed, stimulated by the immune response to various bacterial pathogens such as Streptococcus pyogenes, Staphylococcus aureus, and Pseudomonas aeruginosa. Tissue inflammation induces local hypoxia due to increased oxygen consumption from bacterial infection and the migration/proliferation of immune cells at the infection site. Bacterial components like outer membrane proteins or LPS from Escherichia coli upregulate HIF-1α levels. Additionally, cytokines released post-infection, such as interleukins (IL-6, IL-4, IL-12, IL-1) and tumour necrosis factor-alpha (TNF-α), also contribute to increased HIF-1α expression.

In viral sepsis, elevated levels of HIF-1α are observed in response to viral infections. Certain viruses can accumulate HIF-1α by inhibiting prolyl hydroxylase (PHD) degradation pathways. Activated inflammatory pathways during the immune response can also induce higher HIF-1α levels. Pattern recognition receptors (PRRs) activate innate immunity, triggering inflammatory responses and HIF-1α production. Finally, some respiratory viruses can directly damage lung tissue, causing hypoxia and further elevating HIF-1α levels.

Hypoxia plays a crucial role in shaping the host microenvironment during fungal infections. Infection foci or biofilms formed by host cells and fungi lead to localised hypoxia, worsened by vascular damage reducing oxygen delivery. This oxygen scarcity triggers a hypoxic response in fungi, increasing levels of HIF-1α. HIF-1α assumes a protective role in fungal infections, reducing Candida albicans colonisation in the gastrointestinal tract. Additionally, upregulation of HIF-1α alleviates airway inflammation in mouse models exposed to Aspergillus fumigatus.

Sepsis triggers an immune response through the recognition of microbial products and endogenous danger signals by the complement system and cell-surface receptors, leading to inflammatory dysregulation. Pathogen-associated molecular patterns (PAMPs) from invading microorganisms initiate immune responses, releasing inflammatory factors and activating the innate immune system. Additionally, injuries like sepsis, trauma, and burns release endogenous pattern recognition receptor agonists called damage-associated molecular patterns (DAMPs), further inducing inflammation. These interlocking positive feedback loops between PAMPs, DAMPs, and their receptors underlie the systemic inflammatory response to infection or tissue damage. Inflammatory factors modulate HIF-1α levels, influencing various physiological and pathological processes.

Recent clinical studies have aimed to translate HIF-1α research findings into clinical applications, particularly in post-diagnostic and prognostic aspects of sepsis. Prospective studies have shown significantly elevated levels of HIF-1α mRNA in the blood of shock patients compared to healthy volunteers, indicating its potential diagnostic relevance. Similarly, serum HIF-1α levels in intensive care patients have demonstrated diagnostic potential in sepsis, with significantly higher concentrations detected in patients with septic shock and septic non-shock compared to those undergoing elective surgery. Combining HIF-1α with other clinical parameters has shown high diagnostic accuracy for sepsis, revealing a U-shaped relationship between HIF-1α levels and ICU mortality.

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HIF-1α plays a critical role in sepsis, activated not only by intracellular hypoxia but also by the inflammatory process and immune regulation. Its activation governs the host's adaptive response to hypoxia during sepsis and influences the release of inflammatory mediators and the balance between anti-inflammatory and immune tolerance states. Additionally, HIF-1α activation regulates various pathophysiological processes such as mitochondrial function and apoptosis. Future studies can delve into the molecular mechanisms and pathways of HIF-1α in sepsis, potentially revealing new targets and strategies for the early diagnosis and treatment of this condition.

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