6 Pro-survival Phenotype of HIF-1α: Neuroprotection Through Inflammatory Mechanisms

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Abstract

Hypoxia-inducible factor 1 (HIF-1) is a major player in the oxygen sensor system as well as a transcription factor. HIF-1 is also associated in the pathogenesis of many brain diseases including Alzheimer's disease (AD), epilepsy and stroke. HIF-1 regulates the expression of many genes such as those involved in glycolysis, erythropoiesis, angiogenesis and proliferation in hypoxic condition. Despite several studies, the mechanism through which HIF-1 confers neuroprotection remains unclear, one of them is modulating metabolic profiles and inflammatory pathways. Characterization of the neuroprotective role of HIF-1 may be through its stabilization and the regulation of target genes that aid in the early adaptation to the oxidative stressors. It is interesting to note that mounting data from recent years point to an additional crucial regulatory role for hypoxia-inducible factors (HIFs) in inflammation. HIFs in immune cells regulate the production of glycolytic energy as well as innate immunity, pro-inflammatory gene expression, and mediates activation of pro-survival pathways. The present review highlights the contribution of HIF-1 to neuroprotection where inflammation is the crucial factor in the pathogenesis contributing to neural death. The potential mechanisms that contribute to neuroprotection as a result of the downstream targets of HIF-1α are discussed. Such mechanisms include those mediated through IL-10, an anti-inflammatory molecule involved in activating pro-survival signaling mechanisms via AKT/ERK and JAK/STAT pathways.

Keywords

HIF-1α · Neuroinflammation · Neuroprotection

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6.1 HIF-1 in Hypoxia and Inflammation

Under various pathologies and metabolic conditions, hypoxia and inflammation appear to have a complex interaction [1, 2]. The formation of hypoxic signaling intermediates are known to accompany inflammatory conditions, which in turn initiate inflammatory responses by activating cytokines and inflammatory cells [3]. In the recent years HIF-1 has been described to be a significant modulator of hypoxia signaling in inflammation. HIF-1 is a heterodimeric protein complex that plays a significant role in responding to low concentrations of oxygen or hypoxia and is constitutively expressed as a subunit-β and an oxygen-dependent subunit-α. During normoxic conditions, HIF-1α is synthesized and degraded by the ubiquitin-proteasome system [2]. Oxygen-independent mechanisms can also regulate HIF-1 transcription and translation under normoxia during altered metabolic states. Thus, HIF-1 is a crucial transcriptional factor that regulates thousands of genes for maintaining cellular homeostasis. This process is crucial for the survival and function of immune cells by regulating gene transcription. It has been observed that the blood levels of inflammatory cytokines such IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) are elevated in hypoxia conditions [4]. Intriguingly, HIF-1 stability has shown to regulate the production of inflammatory cytokines like TNF-α and as a result inflammation and hypoxia signaling augment one another through a positive feedback loop [5–7].

Mechanism and Role of HIF-1α in Pathophysiology HIF-1α may be the major contributor behind beneficial and deleterious effects throughout the emergence of the most important dysfunctionality connected to neurodegeneration. Depending on the degree of hypoxia, HIF-1α has been shown to play a dual role as a "protective transcription factor" or a "killing factor" (when linked to p53) [8]. Once HIF-1α is stabilized, the HIF-1 complex is subsequently moved into the nucleus where it acts as a transcriptional activator for over thousands of genes [9]. The activation of HIF-1α during moderate hypoxia can enhance tolerance to a more severe hypoxic lesion later on and thus enable the adaptive changes needed for a quicker and better recovery of the afflicted tissue. HIF-1 functions as an endogenous biological defense mechanism that confers protection against global cerebral ischemia or potential fatal damages under ischemic conditions [10]. Additionally, it has been shown that HIF-1 is up-regulated in a variety of disorders, including several neurological diseases, as a brain neuroprotective response element against stresses including reactive oxygen species (ROS) and inflammation [11].

HIF-1α and Inflammation in Neurological Disorders Inflammation is known to exacerbate disease related pathologies by releasing pro-inflammatory cytokines IL-1β, IL-6 and triggering ERK1/2/AKT, JNK/MAPK and JAK/STAT signaling pathways and thus resulting in severe neural dysfunctionality. Neurological disorders such as Alzheimer's disease (AD), epilepsy, amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and stroke are characterized by progressive loss of neural functions. During pathogenesis of neurological disorders, the inflammatory cytokines, including as macrophage-derived TNF-α and IL-1β, upregulate HIF-1 through mechanisms that inhibit prolyl hydroxylase (PHD) enzymes and increase HIF-1 stability and transcriptional activity [12–14]. Additionally, HIF-1 may inhibit the production of pro-inflammatory cytokine receptors, which reduces the dangers of severe neuroinflammation during ischemic insult [15]. HIF-1α-mediated down regulation of pro-inflammatory cytokines such as IL-6 and TNF-α has been recently described to act through IL-10-mediated attenuation of NLRP3 inflammasome or via IL-10/JAK1/STAT3-mediated transcriptional attenuation [16, 17]. IL-10-mediated immune regulation occurs through the downregulation of pro-inflammatory cytokines. IL-10-mediated inflammatory pathways have been studied for its implications in the design of targeted approaches aiming at controlling deleterious inflammation in

the brain [18]. Additionally, IL-10 receptor activation has been shown to specifically activate the JAK1-STAT3-mediated downregulation of pro-inflammatory cytokines [19, 20]. Further, IL-10/JAK1/STAT3 pathway has been described as the negative regulator of inflammation that controls both the degree and duration of inflammation [21, 22].

6.2 Inhibition of NLRP3 Inflammasome by HIF-1α

Activation of the NLRP3 inflammasome plays a crucial role in the outcome of various brain diseases and injury such as Alzheimer's and traumatic brain injury [23]. The authors describe that the contribution of NLRP3 inflammasome is associated with cellular damage and increased inflammatory responses following traumatic brain injury. Furthermore, blocking or inhibiting the activation of the NLRP3 inflammasome may have substantial potential to salvage tissue damage during traumatic brain injury. The binding of HIF-1α to IL-10 promoter has been reported to be involved in HIF-1α-mediated IL-10 expression and its role in modulation of cell metabolism and inflammatory responses. Reports have shown that HIF-1α stabilization elicits a neuroprotective response through modification of inflammatory pathways via modulation of cytokine regulation. Figure 6.1 shows a proposed scheme of the mechanisms of how HIF-1α mediates downstream inflammatory pathways. Once HIF-1α is stabilized, it acts to activate the JAK-STAT3 pathways and/or inhibit the NLRP3 inflammasome, and thus resulting in neuroprotection. Diet-induced stabilization of HIF-1α and upregulation of IL-10 in rodent brain under normoxic ketotic conditions has been shown to play a role in the upregulation of the IL-10 and downregulation IL-6 and TNF-α [17, 24, 25, 26], whereby HIF-1α transcriptionally regulates IL-10 levels by direct binding to hypoxia responsive elements (HREs) on the IL-10 promoter [24, 27]. Recent studies bring together ketosis-mediated stabilization of HIF-1α as a potential neuroprotective phenotype in mice and rats in an oxygen-independent manner via IL-10-mediated activation of JAK1-STAT3, AKT/ERK pathways [17, 28].

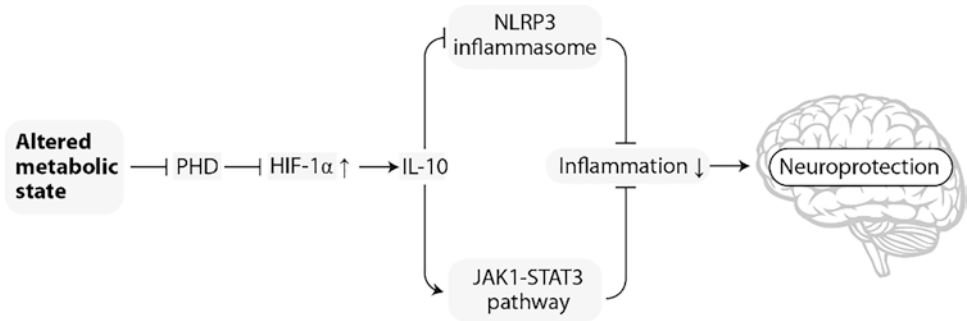

Fig. 6.1 Neuroprotective Phenotype & HIF-1α. Working model of IL-10-mediated JAK1-STAT3 pathway activation following HIF-1α stabilization through a metabolic induced inhibition of prolyl hydroxylase (PHD). Accumulation of HIF-1α as a result of an altered metabolic state activates IL-10, whereby resulting in an upregulation of pro-survival pathways involving JAK1-STAT3, ERK/AKT and inhibition of NLRP3 inflammasome

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