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Review

The hypoxia-inducible factor (HIF) couples immunity with metabolism

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ABSTRACT

Crosstalk between metabolic and immune pathways has recently become appreciated to be key to the regulation of host defence. The hypoxia-inducible factor (HIF) is a transcription factor which was initially described as a ubiquitous master regulator of the transcriptional response to hypoxia. In this role, HIF regulates genes promoting adaptation to hypoxia including a number which influence the cellular metabolic strategy of a cell. It has more recently been appreciated that the regulation of HIF is not restricted to oxygen-dependent pathways, and is now known to be mediated by a number of additional metabolic and immune cues including metabolites and cytokines respectively. Furthermore, our understanding of the functional role of HIF has expanded to it now being appreciated as a major regulator of host immunity. This places HIF in an ideal position to act as a regulatory hub which links metabolic activity with immunity. In this review we synthesise recent data which identifies HIF as both a target and effector for metabolic and immune processes. Developing our understanding of the role of HIF in this context will uncover new therapeutic targets for inflammatory and infectious disease.

Contents

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1. Introduction

1.1. Immunometabolism

Our growing appreciation of the interdependent relationship which exists between metabolism and immunity has led to the emergence of immunometabolism as an independent field of study [1,2]. The concept of immunometabolism is based on the observation that in order to mount an effective immune response, significant alterations in immune cell metabolism must first occur and immunity is heavily under the influence of multiple metabolic cues (which we term here immunometabolites). Conversely, during inflammation, immune signals play a crucial role in regulating metabolism through the activation of key signalling pathways [3]. Therefore a high degree of bidirectional dialogue between metabolic and immune pathways is required for effective host defence.

The process of immune cell activation exemplifies the crosstalk between immunity and metabolism. For example, undifferentiated T cells and monocytes are relatively quiescent cells whose primary objective in terms of energy homeostasis is to produce sufficient ATP to meet basic cellular survival demands. In response to infection however, these cells are required to rapidly differentiate and proliferate, thereby creating a large increase in energy demand [4]. In order to satisfy this demand, activated immune cells rapidly adjust their metabolic strategy [5]. This metabolic reprogramming centres on a shift towards 'aerobic glycolysis' (the Warburg effect). As well as boosting cellular ATP production, a number of the metabolites of glycolysis can be used as precursors for the biosynthesis of lipids, nucleotides and amino acids [6]. The metabolic strategy adopted by an immune cell has significant implications for differentiation [7]. For example, a more heavily glycolytic state skews macrophage and T cell differentiation to M1 and Th17 respectively [8]. Therefore immune and metabolic pathways are in close communication during immune cell activation, differentiation and proliferation.

A second example of the close association between metabolism and immunity occurs during an active inflammatory response where the influx of neutrophils (which consume large amounts of oxygen to facilitate the antibacterial oxidative burst) renders inflamed tissues hypoxic [9,10]. This depletion in oxygen levels signals rapid changes in metabolic strategy in order to promote cellular survival during this hypoxic exposure [11,12]. While reduced tissue oxygenation during inflammation was reported as early as the 1930s [13], it was not until the discovery of the oxygen sensitivity and immune regulatory roles of the transcriptional regulator hypoxia-inducible factor (HIF) that we began to appreciate the functional importance of this inflammatory hypoxia [14–16].

In this review, we will discuss the nature of the signalling links which exist between metabolism and immunity and the potential that these pathways have as new therapeutic targets in inflammatory and infectious disease. HIF is a key transcriptional pathway which is downstream of multiple metabolic and immune signals and can in turn regulate both metabolism and immunity. While additional pathways are also likely involved in immune/metabolic crosstalk, in this review we will focus on the role of HIF, how it is affected by metabolic and immune signals and the consequences of its activation for host defence.

1.2. The hypoxia–Inducible factor (HIF)

Oxygen is critically important for cell, tissue and organism survival as its chemical reduction during oxidative phosphorylation by the mitochondrial electron transport chain is the primary mechanism of ATP production in eukaryotic cells [17,18]. Due to the reliance on a constant supply of oxygen for survival, it is unsurprising that metazoans have evolved mechanisms to sense hypoxia and elicit responses aimed at the maintenance of oxygen homeostasis during times of hypoxic stress. HIF is a master regulator of oxygen homeostasis which allow cells to adapt and to survive periods of hypoxia [16]. The HIF transcription factor family consists of heterodimeric proteins composed of an oxygen-liable HIF-α subunit (HIF-1α, HIF-2α or HIF-3α) and a constitutively expressed HIF-1β subunit. In normoxic conditions, HIF-α subunits are hydroxylated by oxygen-dependent hydroxylases known as prolyl hydroxylases (PHDs) [17]. HIF hydroxylation results in recruitment of the von Hippel-Lindau (pVHL) protein resulting in the formation of an E3 ubiquitin ligase complex that targets HIF-α for proteasomal degradation [17]. The transactivation domain of HIF-α is also repressed in normoxic conditions by an asparagine hydroxylation catalysed by Factor Inhibiting HIF (FIH) which prevents the association of HIF-α with the p300 coactivator [19]. In hypoxic conditions, HIF-α is rapidly stabilised, dimerizes with HIF-1β and forms a functional transcriptional complex with p300 due to inactivation of the oxygen-sensitive hydroxylases. This heterodimer then translocates to the nucleus to activate the transcriptional adaptive response to hypoxia. Target genes for HIF include genes involved in the promotion of angiogenesis, erythropoiesis and the regulation of metabolism (including the promotion of glycolysis and the suppression of oxidative phosphorylation) [20–23].

2. What regulates HIF?

2.1. Metabolic cues which regulate HIF

Because mitochondria are the central hubs of cellular metabolism, changes in metabolic activity result in a number of signals emanating from these organelles which regulate the HIF pathway (Fig. 1). These regulatory links between altered metabolic activity and HIF are being increasingly recognized as essential pathways for the execution of effective host immunity. Importantly, the nature of these signals is dependent upon the nature and degree of flux through the metabolic pathways utilized in a specific context. Therefore, they can change to reflect metabolic status and act in a controlled and dynamic manner allowing metabolic control of immunity. A number of signals which can strongly regulate HIF activity emanate from the mitochondria in a manner which reflects the metabolic status of the cell, including the following:

2.1.1. Oxygen

The rate of oxygen consumption by cells is dynamic and depends upon the energy (ATP) demands that a cell has in a specific context [18]. Under normal physiologic conditions (normoxia), the oxygen available to a cell usually exceeds the demands of oxidative metabolism [24]. As well as acting as an "oxygen reservoir", this spare, non-mitochondrial oxygen signals a state of normoxia to transcriptional pathways including (but not limited to) HIF. The