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Review

Glucose Metabolism in T Cells and Monocytes: New Perspectives in HIV Pathogenesis

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ABSTRACT

Activation of the immune system occurs in response to the recognition of foreign antigens and receipt of optimal stimulatory signals by immune cells, a process that requires energy. Energy is also needed to support cellular growth, differentiation, proliferation, and effector functions of immune cells. In HIV-infected individuals, persistent viral replication, together with inflammatory stimuli contributes to chronic immune activation and oxidative stress. These conditions remain even in subjects with sustained virologic suppression on antiretroviral therapy. Here we highlight recent studies demonstrating the importance of metabolic pathways, particularly those involving glucose metabolism, in differentiation and maintenance of the activation states of T cells and monocytes. We also discuss how changes in the metabolic status of these cells may contribute to ongoing immune activation and inflammation in HIV- infected persons and how this may contribute to disease progression, establishment and persistence of the HIV reservoir, and the development of co-morbidities. We provide evidence that other viruses such as Epstein–Barr and Flu virus also disrupt the metabolic machinery of their host cells. Finally, we discuss how redox signaling mediated by oxidative stress may regulate metabolic responses in T cells and monocytes during HIV infection.

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1. Introduction

Cells comprising the immune system are conditioned to respond rapidly and vigorously to antigenic and inflammatory signals, a process that heightens cellular metabolism and requires energy. Experiments using cell culture systems show that the glucose transporter Glut1, an integral membrane protein that mediates glucose uptake into the cell, is required for efficient HIV infection of CD4 + T cells (Loisel-Meyer et al., 2012) and is a marker of CD4 + T cell metabolic activity (Palmer et al., 2014a). Moreover, the number of CD4 + T cells that express Glut1 is increased in HIV-infected, treatment-naïve persons. This was reduced during suppressive antiretroviral therapy (ART) but was not completely normalized when compared to uninfected individuals. High circulating levels of these cells is associated with immune activation and a low CD4 + T cell count in patients, irrespective of treatment status (Palmer et al., 2014a). Macintyre and co-workers have demonstrated that Glut1 is required for CD4 + T cell activation and effector functions, and that Glut1 is critical for the transitioning from oxidative phosphorylation to aerobic glycolysis (Macintyre et al., 2014). Additionally, Oestreich et al., have recently shown that glycolysis is tightly controlled by the transcription repressor Bcl-6, which suppresses genes encoding molecules important in the glycolytic pathway in T cells (Oestreich et al., 2014). This demonstrates additional levels of metabolic control other than the canonical PI3K–Akt–mTOR axis, an intracellular signaling pathway that regulates glucose metabolism post-transcriptionally (Powell et al., 2011; MacIver et al., 2013; Palmer et al., 2015a).

Despite increasing awareness regarding the significance of HIV and growth cytokines in regulating glucose metabolism (Loisel-Meyer et al., 2012; Palmer et al., 2015b; Locasale and Cantley, 2011; Dagenais-Lussier et al., 2015), the physiological control of metabolism in immune cells in HIV infected persons has not been thoroughly investigated. However, new evidence indicates that intracellular redox state may exert metabolic control in T cells and monocytes during HIV infection (discussed in detail below). Indeed, it has long been proposed that augmented oxidative stress in HIV-infected individuals leads to accelerated disease progression, leading to suggestions that antioxidants might have a role in improving patients' health (Kotler, 1998). This review will discuss the recent advances in immunometabolism in the context of HIV and discusses how redox signaling may regulate key metabolic checkpoints in T cells and monocytes during HIV infection.

2. The Role of Glucose Metabolism in HIV Pathogenesis

2.1. Glucose Metabolism in CD4 + T Cells During HIV Infection

Data showing that CD4 + T cell metabolic activity is critical for HIV infectivity and immune activation is now gaining greater impact with increasing evidence that T cell activation shares an intimate association with metabolism (Hegedus et al., 2014). The well-established dogma is that activated CD4 + T cells are preferential targets for HIV infection. Activation of CD4 + T cells is accompanied by metabolic reprogramming which involves a switch from oxidative metabolism in resting cells to intensified glucose metabolism via aerobic glycolysis (Palmer and Crowe, 2012). Indeed, Macintyre and colleagues have revealed that Glut1 is essential for metabolic programming of CD4 + T cell activation, expansion and survival (Macintyre et al., 2014). Glycolysis results in the production of pyruvate from glucose with only a net of two adenosine triphosphates (ATPs) per molecule of glucose. By contrast if pyruvate proceeds through the tricarboxylic acid cycle (TCA cycle) to oxidative phosphorylation, an additional 36 ATP molecules are produced. This suggests a rather inefficient utilization of glucose, energetically, by activated CD4 + T cells which have a markedly increased demand for energy. Glycolysis also diverts the use of glucose for macromolecular biosynthesis essential for cell growth, proliferation, differentiation and maintenance of an activated state (MacIver et al., 2013). Distinct metabolic programming will also affect the levels of metabolites that can directly regulate immune cell functions (Loftus and Finlay, 2016).

The significance of glucose metabolic pathways in regulating HIV infection in CD4 + T cells has long been recognized. Early work by Sorbara et al. hinted at the significance of glucose metabolism in HIV infection by demonstrating that HIV infection of the H9 human T cell line induced the expression of Glut1 and Glut3 and increased glucose uptake (Sorbara et al., 1996). Further support came from Hollenbaugh and colleagues who found that HIV infection of primary CD4 + T cells in culture resulted in increased glucose uptake and expanded levels of glycolytic intermediates (Hollenbaugh et al., 2011). More link between glucose metabolism and HIV infection was established by Loisel-Myer et al., who showed that increased Glut1 expression on CD4 + T cells in culture increased cellular permissivity to HIV-1 infection, and that suppression of glucose metabolism by PI3K inhibitors inhibited infection (Loisel-Meyer et al., 2012). Although Loisel-Myer's group utilized LY294002, the non-selective isoform and non-tissue specific PI3K inhibitor, their results demonstrated that the PI3K pathway at least in part regulates glucose metabolism in CD4 + T cells. The PI3Kγ isoform has been proposed as potentially involved in glucose metabolic regulation in immune cells, but it's involvement in HIV infectivity is unclear (Palmer et al., 2015b). The significant relationship between metabolism in immune cells and HIV pathogenesis in humans has been elegantly reviewed recently by Dagenais-Lussier and co-workers. They proposed that dysregulated metabolism including excessive uptake of glucose by immune cells could induce hyper-immune activation which may result in HIV-related complications (Dagenais-Lussier et al., 2015).

2.2. Link Between Glucose Metabolism in T Cells and HIV Disease Progression

Inflammatory activation of T cells is accompanied by increased energy requirements via glycolysis, needed for the surge in cytokine production and differentiation into Th1 and Th17 cells. Evidence reveal that the glycolytic intermediate can directly control immune functions. It