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Review

Metabolic reprogramming & inflammation: Fuelling the host response to pathogens

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ABSTRACT

Successful immune responses to pathogens rely on efficient host innate processes to contain and limit bacterial growth, induce inflammatory response and promote antigen presentation for the development of adaptive immunity. This energy intensive process is regulated through multiple mechanisms including receptor-mediated signaling, control of phago-lysomal fusion events and promotion of bactericidal activities. Inherent macrophage activities therefore are dynamic and are modulated by signals and changes in the environment during infection. So too does the way these cells obtain their energy to adapt to altered homeostasis. It has emerged recently that the pathways employed by immune cells to derive energy from available or preferred nutrients underline the dynamic changes associated with immune activation. In particular, key breakpoints have been identified in the metabolism of glucose and lipids which direct not just how cells derive energy in the form of ATP, but also cellular phenotype and activation status. Much of this comes about through altered flux and accumulation of intermediate metabolites. How these changes in metabolism directly impact on the key processes required for anti-microbial immunity however, is less obvious. Here, we examine the 2 key nutrient utilization pathways employed by innate cells to fuel central energy metabolism and examine how these are altered in response to activation during infection, emphasising how certain metabolic switches or 'reprogramming' impacts anti-microbial processes. By examining carbohydrate and lipid pathways and how the flux of key intermediates intersects with innate immune signaling and the induction of bactericidal activities, we hope to illustrate the importance of these metabolic switches for protective immunity and provide a potential mechanism for how altered metabolic conditions in humans such as diabetes and hyperlipidemia alter the host response to infection.

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Recently, historically recorded observations regarding changes in immune cell metabolism have been linked to immune function, differentiation and activation in response to signals. Nutrient utilization has long been a distinguishing feature of cells of the innate immune system, in particular linked to the production of reactive oxygen and nitrite species critical for anti-microbial host defence. Although classification of cellular phenotypes has traditionally been based on the expression patterns of key enzymes involved in these pathways – for example the expression of inducible nitric oxide synthase (iNOS) versus arginase-1 in "M1/classically activated" or "M2/alternatively activated" macrophages – it is emerging now that the production, amounts and turnover of metabolic substrates themselves influence not just how the cell utilizes nutrients and generates energy in the form of ATP, but also drives key signaling events through multiple mechanisms. In particular, a central bio-energetic pathway observed in most cells, metabolism of glucose to drive oxidative phosphorylation (OXPHOS) in the mitochondria, and its alternative metabolism to lactate via anaerobic glycolysis or aerobic glycolysis, has emerged as a key immune-metabolic axis influenced by and determining immune cell function, particularly linked to excessive inflammation and the pathogenesis of sepsis. The balance of lipids and the pathways which regulate their turnover are also known to engage inflammation in the pathogenesis of metabolic diseases including diabetes, obesity and atherosclerosis. Less well understood, however, is how important these events are in driving protective immunity and in regulating host anti-microbial defence mechanisms. In this review, we will summarise the work examining metabolic pathways influencing innate immune pathways and link these to key anti-microbial functions, with a particular focus on macrophages, whose phenotypic and metabolic plasticity during inflammatory responses makes them particularly amenable to metabolic manipulation to drive protective immunity and develop targeted host-directed immunotherapy.

We begin by summarising the changes in central energy metabolism that impact upon host responses to infection, with an emphasis on the pathways which utilise glucose and lipids as their carbon-source, before examining how metabolic shifts intersect and fuel these defence mechanisms.

1. Metabolic reprogramming in activated immune cells

1.1. Glucose metabolism

1.1.1. Overview of central energy metabolism

Cell energy metabolism refers to the process by which biochemicals are used to generate energy (in the form of ATP). The preferred carbon source for mammalian cells, glucose, is reduced to Pyruvate via the regulated multi-enzyme Glycolysis pathway, with Pyruvate entering the mitochondrion to feed the Tricarboxylic Acid (TCA) cycle (Fig. 1). Alternatively, catabolism of fatty acids can generate acetyl-coA to feed the citric acid cycle and ATP generation through a process known as β-oxidation. The TCA cycle is a multi-step oxidative process which sequentially generates a number of carbon intermediates within the mitochondrial matrix, with simultaneous generation of NADH and $FADH_2$. These reducing agents feed the electron transport chain (ETC) on the inner mitochondrial membrane at Complex I and Complex II, respectively, driving electron transfer that is coupled to pumping of protons from the mitochondrial matrix to the inter-membrane space. This creates an electrochemical proton gradient (ΔY) that can be harnessed by ATP synthase to drive production of large amounts of ATP (36–38 molecules of ATP per glucose molecule). Electrons transferred along the ETC are eventually used in the generation of water from molecular Oxygen. Thus, OXPHOS absolutely requires Oxygen. In the absence of Oxygen, Pyruvate does not enter the mitochondrion, but is instead metabolised to Lactate in the cytoplasm, with Glycolysis rapidly providing small amounts of ATP (2 molecules of ATP per glucose molecule) to meet energy requirements. However, multiple biological processes have been described where Pyruvate is preferentially metabolised to Lactate despite availability of Oxygen, a process termed "Aerobic Glycolysis". This metabolic switch to Aerobic Glycolysis, or "Glycolytic Reprogramming", is now well-recognised in activated immune cells, occurring alongside switches in lipid metabolism and amino acid metabolism, all of which have emerged as key mediators of immune function.

1.1.2. Immune cell activation

Though not formally recognised, the process of metabolic reprogramming in immune cells has been reported since mid-1900s, with elevated rates of glucose utilization and aerobic glycolysis seen in neutrophils [1–3], monocytes [4], macrophages [5–9] and lymphocytes [10] following stimulation, prompting speculation that aerobic glycolysis allowed accumulation of metabolic intermediates that could act as precursors for macromolecule synthesis [11]. The link between glycolytic reprogramming and anti-bacterial functions in neutrophils were postulated as far back as 1980. Increased flux through the parallel pentose phosphate pathway (PPP) (that occurs in concert with increased flux through the glycolytic pathway) was observed to generate the reducing equivalent NADPH and, coupled with increased non-mitochondrial oxygen consumption, allowed formation of reactive oxygen species (ROS) important for neutrophil-mediated killing