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How host metabolism impacts on virus pathogenesis

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The outcome of virus infections depends on multiple factors. This review deals with the role of host metabolism as one such factor. We describe how different cells in the immune system employ differential metabolic pathways and how this relates to the outcome of virus infections. We also discuss how nutritional and metabolic diseases can influence the nature of viral pathogenesis as well as how targeted therapies against metabolic processes can impact on the outcome of virus infections. The case is also made for metabolic profiling as a potential tool to predict the outcome of a virus infection and to guide therapies that enhance host resistance.

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Introduction

Few if any viruses kill all the hosts they infect but instead cause a broad range of consequences. The outcome is affected by properties of the virus itself, the circumstances of infection (such as dose and route of delivery) and several variables within the host which include genetics, age, and previous experience with other agents and the makeup of microbes that inhabit the gut and other locations [1]. A poorly studied variable that could affect the outcome of virus infections is host metabolism, the topic of this brief review. We strive to answer a number of questions and speculate if manipulating the metabolic status of infected persons could be a useful strategy to shape the consequences of a virus infection.

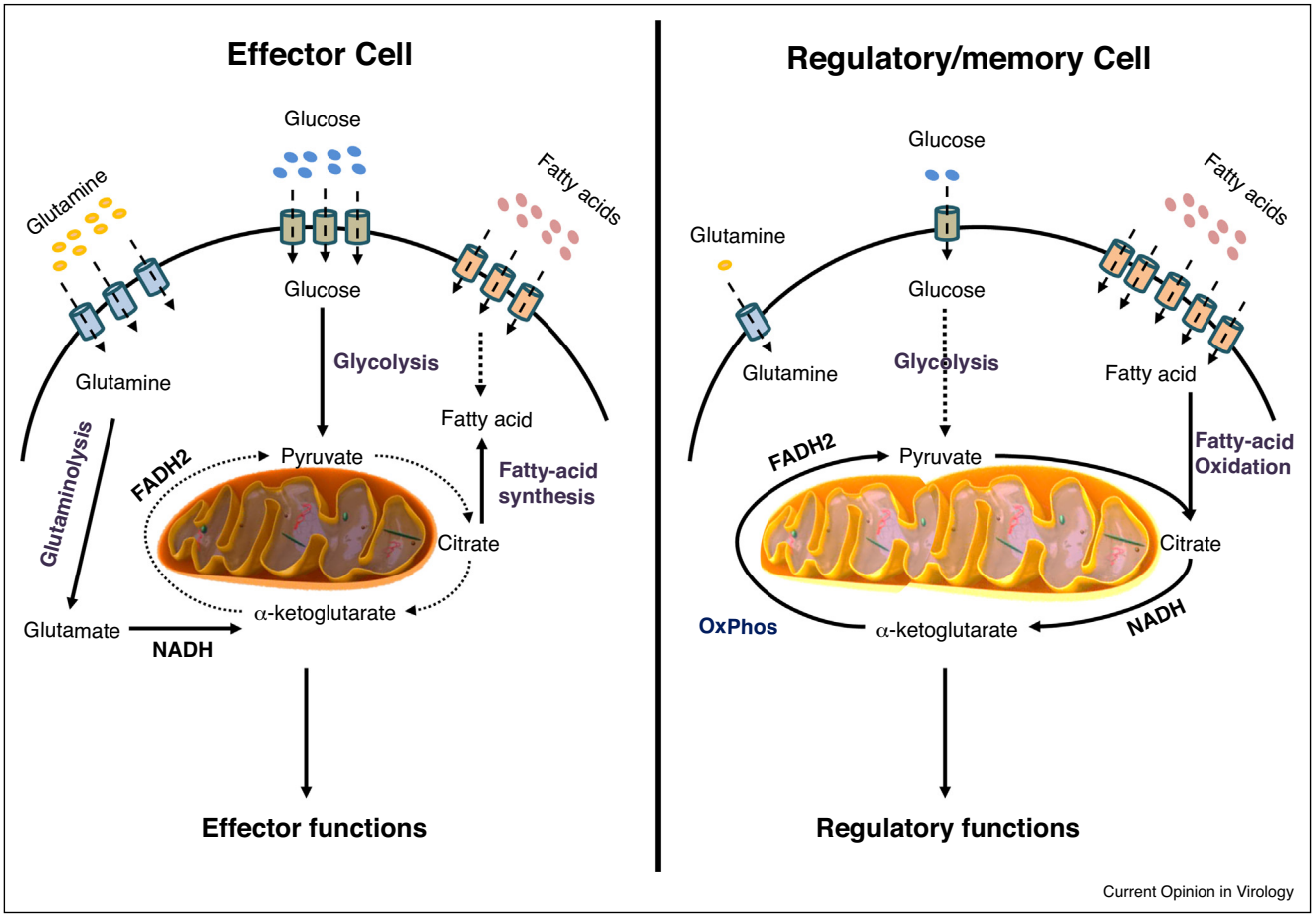
Some lessons to be learned

Immunologists rediscovered their biochemistry of metabolism quite recently and several informative reviews have been written [2,3]. Basically, cellular components of both innate and adaptive immunity adopt different primary means of generating energy and biosynthetic products to support their immune functions. In addition, activated cells responding to immune stimuli reprogram their metabolism and use different pathways compared to those adopted by resting cells. As elegantly recounted by Luke O'Neil, there are six major metabolic pathways which immune cells differentially employ to sub-serve their functions [4•]. These pathways include glycolysis, oxidative phosphorylation, pentose phosphate pathway, fatty acid oxidation, fatty acid synthesis and amino acid metabolism. To date, most investigations have focused on pathways that provide cells with energy, biosynthesis, and redox balance. For instance, naïve T cells, memory T cells and some T cells with regulatory function (Treg) require few nutrients and all use oxidative phosphorylation (oxphos) supported by oxidation of fatty acids to supply their energy. However, activated immune cells that are involved in pathogen clearance and inflammation, such as CD4, CD8 T cells and M1 type macrophages, derive their energy mainly from glucose via aerobic glycolysis [4•]. These effectors also take up amino acids, such as glutamine, to generate intermediates which enter the tricarboxylic acid cycle. This generates products that include coenzymes and fatty acids which provide metabolic precursors for energy and biosynthesis (see Figure 1). Hence, nutrient availability and how they are used by an immune cell becomes a critical issue which helps determine the efficacy of an immune response. A major interest has been to explore how manipulating the balance of oxphos and glycolytic metabolism can be used to shape the course of immune events in autoimmunity and cancers [5], but few studies have related metabolic events to the outcome of infectious diseases. We demonstrate that host metabolism can have a major effect on virus infections and speculate about the value of metabolic profiling to predict the outcome of infections.

Does nutrient availability influence the outcome of virus infection?

It seems logical to assume that malnutrition could affect the outcome of a virus infection and observations have linked starvation, obesity or dietary deficiencies to changes in responses to some virus infections [6,7]. However, at least with human virus infections, the cause and effect evidence is scanty and usually provides no mechanistic explanation for observed changes in susceptibility. It is known that nutritional effects such as increased sugars and fat intake can change the number and function of immune cell types [8,9], but how this relates to the expression of virus infection requires further investigation. One of the more complete studies on nutritional

Figure 1



Metabolic differences in immune cells with effector functions versus cells with regulatory or memory functions. (1) Effector immune cells take up glutamine and glucose to generate ATP and intermediates for amino acids and fatty acid synthesis (2) Regulatory and memory immune cells take up less glucose and glutamine molecules but instead take up more fatty acids that power mitochondria to generate ATP. Dominant metabolic pathways are shown in solid lines; less critical or studied pathways are shown in dotted lines.

consequences to infections was reported by the Medzhitov group [10••]. They evaluated the effects of calorie deprivation and supplementation on the outcome of some viral and bacterial infections in mice. They showed that deprivation increased susceptibility to a neurotropic strain of influenza virus, yet increased resistance to bacterial infections. In addition, force-feeding with extra glucose saved the mice from virus infection, but made them more susceptible to bacteria. They associated these effects with glucose metabolism, since inhibiting glucose utilization with 2-deoxy glucose (2DG) led to virus-induced lethality, but survival from bacterial infection. This outcome did not correlate with effects of 2DG on immune responsiveness, but was attributed to effects on ER stress responses in the brain to virus-induced interferon induction. This uncontrolled ER stress response resulted in neuronal apoptosis through induction of a pro-apoptotic protein — CHOP. Thus, inhibition of glucose utilization during virus infection led to CHOP dependent death of mice. Additionally, in a system using poly (I:C) to mimic a virus infection, animals treated with 2DG also succumbed to a similar ER stress mediated apoptotic response in the CNS [10••].

Another example where inhibition of glucose utilization led to severe consequences was observed following ocular HSV infection in mice [11•]. When treated with 2DG during acute infection, the majority of animals developed lethal encephalitis and virus was present in the CNS. The outcome was proposed to result from inadequate control of virus replication at the infection site because of suppressed innate immunity, along with less efficacious CD8 T cell control of virus in the local nerve ganglia.

There are situations where impaired glucose utilization can limit the damage caused by a virus infection. Such a circumstance was observed where virus caused tissue lesions by an immunopathological mechanism [11•].