Review

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Role of metabolism during viral infections, and crosstalk with the innate immune system

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Summary **Viruses have been for long polemic biological particles which stand in the twilight of being living entities or not. As their genome is reduced, they rely on the metabolic machinery of their host in order to replicate and be able to continue with their infection process. The understanding of their metabolic requirements is thus of paramount importance in order to develop tailored drugs to control their population, without affecting the normal functioning of their host. New advancements in high throughput technologies, especially metabolomics are allowing researchers to uncover the metabolic mechanisms of viral replication. In this short review, we present the latest discoveries that have been made in the field and an overview of the intrinsic relationship between metabolism and innate immunity as an important part of the immune system.**

Keywords: Metabolism, viral infections, metabolomics, innate immune system, virus

1. Introduction

Recently, a number of studies have highlighted the importance of studying metabolism for a better understanding of the infection process caused by many pathogens (*1-6*). In particular, viruses are infective particles that need to take advantage of the host metabolism, hijacking the cellular machinery in order to replicate (*4,6,7*), and that has also been demonstrated for viruses in other species (*8,9*). These new approaches have uncovered different mechanisms used by the viruses to continue their life cycle, and raise the possibility that these altered pathways could become new therapeutic targets in order to treat viral infections (*4,7,10*).

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Central metabolism is a key element for the immune system as well (*11*). One of the branches of the immune system, innate immunity, is one of the first lines of defence in case of an infection process, and for example, metabolic programmes for polarized macrophages are completely different (*12*). Given the importance of understanding the players involved during infection, a broad perspective is presented here.

The focus of this review will be first over the described perturbations that viral infections have over the host metabolism, and second will describe the recognized importance of metabolism for the innate immune system.

2. Metabolomic effects of viral infection

The complexity of viruses still fuels the debate about if they are living entities or not (*13*), due to their differences with other types of unicellular or multicellular organisms. One of the confounding features, is the need of an ordered enzymatic environment (*14*), as viruses depend on the host metabolism in order to perform the necessary events

Table 1. Metabolic effects of viral infections

Virus	Metabolic effect	*Ref.*
VACV, DENV	Alteration of glycolysis, FAS, and glutaminolysis	(*15*)
HCMV	*de novo* pyrimidine biosynthetic flux in host cells	(*4*)
HCMV, influenza A	Inhibition of FAS, suppression of replication HCMV and influenza A	(*27*)
HCMV	Infection requirement of long chain FA metabolism: acyl-CoA synthetases and fatty acid elongases	(*18*)
KSHV	Inhibition of FAS and decrease in number of lytic enveloped viruses, induced apoptosis infected cells	(*10*)
EBV, VZV, poliovirus, HCV	Inhibition of FAS, lower number of infectious virus	(*2,32-35*)

This table summarizes the main effects that viral infections have over metabolism. VACV: vaccinia virus; DENV: Dengue virus; HCMV: Human Cytomegalovirus; KSHV: Kaposi's Sarcoma-associated herpesvirus; EBV: Epstein-Barr virus; HCV: Hepatitis C virus; FA: Fatty Acids; FAS: Fatty Acids Synthesis; TCA: tricarboxylic acid cycle.

leading to their replication (*15-19*), while that process by itself requires high amounts of energy in a very short period of time (*3*). The energy requirement and dependence on the host metabolism, is especially important in viruses with a limited coding capacity, *e.g*. Dengue Virus (DENV) (*20*). The latter has been reported for several viruses, in a number of studies reviewed by Sánchez and collaborators (*3*). Among others, the main altered metabolic pathways are glycolysis, fatty acid synthesis (FAS), and glutaminolysis (*3*).

These ideas have been previously summarized by Fontaine (*15*) (Table 1), where she performed different analysis of the effect of the infection of vaccinia virus (VACV) and DENV over the human cellular metabolome, using high-throughput metabolomic approaches. The Warburg effect (aerobic glycolysis), has also been reported upon viral infections (*21,22*). Similarly to what happens in cancer cells, the system carries out a higher rate of glycolysis, instead of using the more cost-effective tricarboxylic acid (TCA) cycle for the generation of energy. Although TCA is not shut-down, it works at a lower rate than in normal conditions, resulting in increased levels of lactate. On the exploration of metabolomic alterations upon viral infections, DeVito and collaborators (*4*) (Table 1) have studied human fibroblasts infected with Human Cytomegalovirus (HCMV), finding that infection induced a *de novo* pyrimidine biosynthetic flux in the host cells, which is required to maintain uridine diphosphate glucose (UDP-glucose), and glycosylation of a virion protein. Interestingly, when inhibiting pyrimidine biosynthesis they observed decreased levels of viral DNA accumulation. As they have addressed, membranes of coated virus include critical glycoproteins for the infection, as occurs for example in infections with hantavirus (HTV). The Gn (or G1 (of 68-76 kDa)) (*23*) and Gc (or G2 (of 52-58 kDa)) (*23*) glycoproteins of HTV mediate the infection and entry into the hosts' cells (*24-26*). This metabolic link is important in diverse viral families, as DeVito and colleagues have pointed out according to their observations. This is a main idea that has been highlighted by other authors as well, for example in the review of Miyake-Stoner (*16*). Sánchez and collaborators (*3*) have additionally suggested that the shift in metabolism could help infected cells to survive, and that can ultimately become an advantage for the virus.

DeVito (*4*) has as well reported an elevated metabolism of lipids of the infected cells within their assays. A similar observation of up-regulation in FAS was reported by Munger (*27*) (Table 1) and Koyuncu (*18*) (Table 1). According to Kelly (*28*), the reduced activity of the TCA cycle (when it is under-regulated) drives citrate into the *de novo* synthesis of fatty acids (FA). Consequently with cell homeostasis, the TCA cycle cannot be completely shut down, and because of that, glutamine is used to replenish the TCA intermediates in an anaplerotic way (*29*). As an example of the shortage of development in this field in viruses responsible for infectious diseases, by the end of 2015 there were no metabolomics studies on the influence of HTV either on the human or on the reservoir (*30*).

There is an evident translational potential for the findings made in this field (*31*), as the modified metabolic pathways could be targeted to decrease the expansion of infection. Very interestingly, there have been reported clinical trials for drugs that target metabolism in cancer (*22*). Some of the experimental results for viruses are those of Delgado and collaborators (*10*) (Table 1), where after inhibition of FAS they describe a decrease in the number of lytic enveloped viruses through induced apoptosis of Kaposi's Sarcoma-associated herpes virus (KSHV) infected cells. They inhibited FAS using two drugs: 5-(Tetradecyloxy)-2-Furoic Acid (TOFA, which inhibits acetyl-CoA carboxylase (ACC1) enzyme) or C75 (which inhibits fatty acid synthase (FASN) enzyme). Interestingly, they further demonstrated that this apoptotic effect induced by inhibition of FAS was specific for infected cells, but not for the control. In the same direction, inhibition of FAS has led to a lower number of infectious viruses (Table 1) in cases of HCMV and influenza virus (*27*), Epstein-Barr virus (EBV) (*32*), varicella-zoster virus (VZV) (*33*), poliovirus (*34*), Hepatitis C virus (HCV) (*2,35*), yellow fever virus, West Nile virus and DENV (*36*).

Table 2. Metabolism of innate immunity cells as well as the main metabolic reactions in the main innate immunity cells

Cell line	Metabolic effect	*Ref.*
Macrophages/DCs	Reduced activity of TCA cycle drives citrate into the de novo synthesis of FA	(*28*)
M1 macrophages	Glycolysis based metabolism, higher glycolytic activity	(*12*,*46*)
M2 macrophages	TCA cycle based metabolism,	(*12*,*46*)
moDCs	Decrease in OXPHOS activity with immunogenicity	(*60*,*28*)
NK	mTOR central role in activation, no increase in glycolysis or OXPHOS after short-term activation	(*66*,*68*)

DCs: dendritic cells; NK: natural killer cells; moDCs: monocyte derived DCs; OXPHOS: oxidative phosphorylation; mTOR: mammalian target of rapamycin.

If we consider again another type of viral infection, that produced by HTV, and that according to CDC (*www.cdc.gov*), there is no current treatment for HTV infections, these findings are quite relevant if this virus disturbs the host metabolism in a similar basis as reported in the mentioned studies. Besides, the fact that those tested drugs are already approved for cancer treatment and the dosage per patient has already been defined, make their use to treat HTV infections more feasible than in the case of developing a totally new drug from scratch.

It is puzzling to find the dramatic increase in lipogenesis during viral infections. One of the first thoughts is that FAS is driven towards the biosynthesis of the viral lipid membrane. By extrapolation we could assume the same for HTV or other similar viruses, which also have a lipid bilayer (*37*). Nevertheless, despite the above mentioned findings and the initial conclusions drawn from some authors, Delgado *et al*. (*10*) have raised questions regarding the decrease of viral numbers, pointing out that it is not consistent with only a block in the viral envelope. According to them, FA molecules are not only restricted to the construction of the viral membrane when the virus is present in the cells. They are also required during membrane production at the Golgi apparatus and endoplasmic reticulum, when protein production increases due to higher metabolic requirements from the virus (*28*). A very interesting contribution from Perera and collaborators (*38*) appeared as an abstract, raising the idea that lipids in DENV infection, are used for modification of physical properties of the lipid bilayer, such as curvature, permeability, or recruitment and assembly of membrane protein complexes. These mechanisms may act in a similar way in the described viruses that alter lipid pathways. If we have in mind that, as indicated by Schountz (*30*), metabolic products (*e.g*. lipids, carbohydrates, among others) are identical between different vertebrate species, it could be extrapolated and suggested that different viral species are using metabolites or altering metabolic pathways in a similar fashion. We can support this hypothesis according to what Emini and Fa (*39*) previously indicated, regarding the necessity of the virus for using host-cell machinery to carry out replication (*40*). Besides, a number of viruses in different organisms depend on the host cellular processes for carrying out their life cycles (*9,41*) or altering them for their own advantage (*42,43*). It is important though, to take into account the observations summarized by Fontaine (*15*): *i*) closely related viruses can perform very divergent metabolic programs; *ii*) the same metabolic perturbations (*e.g*. Fatty Acid Synthesis alteration) may be needed by divergent viruses; *iii*) the metabolic programs induced by viruses are cell specific, according to the capability of viruses to adapt to an unique host environment.

Not only does metabolomics serve as a way to characterize the infection process, or to evaluate the possibility to tailor therapies, but additionally can be used for diagnostic purposes due to its specific profiles for each condition (*44*). It cannot be forgotten that the metabolism is the end point of the system, and thus a reflection of the phenotype (*45*).

3. Crosstalk between metabolism and the innate immune system

Besides what has been summarized above for the different studies on viral alteration of metabolism, we cannot forget that there is crosstalk between the immune system and central metabolism (*46,47*), further reviewed by Cheng and collaborators (*46*). Among the two branches of the immune system, innate immunity represents the first line of defence against external infections (*48*). One of the main cell components of this system are macrophages, which in their polarized state are broadly classified into two types (*49,50*): M1 or classical (pro-inflammatory), or M2 or alternative (anti-inflammatory) macrophages (*28,51-53*). They both need fatty acids for production of cytokines, as those are proteins that have to go through the Golgi apparatus for modifications. Regarding these two types of cells, after activation, M1 or M2 macrophages display a different metabolism, relying heavily on the M1 type in glycolysis (Warburg effect), while M2 macrophages rely on the TCA cycle (*12*) (Table 2). Moreover, immune cells can shift their metabolism depending on the given conditions (*54,55*). In detail, M1 polarization is induced by intracellular pathogens, bacterial cell wall

components, lipoproteins, and cytokines such as IFNγ or TNFα, and a shift into glycolysis would be required for their activation (*28*) (Table 2). According to Kelly M1 macrophages are implicated in inflammatory cytokine secretion and NO production, that leads to effective pathogen killing. M2 on the other hand are activated by fungal cells, parasites, immune complexes, complement, apoptotic cells, macrophage colony-stimulating factor (MCSF), IL4 and IL13 (those two especially), IL10, or TGF-β. Following the paper from Kelly (*28*), in this case oxidative phosphorilation (OXPHOS) is the most representative pathway for M2 activation. These macrophages have high phagocytosis capacity, produce extracellular matrix (ECM), participate in wound healing, as well as in clearance of apoptotic cells. Roszer (*52*) indicates that macrophages synthesize lipid derivatives with anti-inflammatory effects, most probably in the M2 population.

As indicated by Cheng (*46*) a Warburg effect can be observed in active state macrophages, and according to Zhu (*12*) this is nothing other than the M1 macrophage state. Cheng (*46*) (Table 2) has also addressed that M1 macrophages are pro-inflammatory and posses higher glycolytic activity, while M2 are anti-inflammatory, and use oxidative glucose metabolism as the principal metabolic pathway to obtain energy in a sustained way. One of the measurable metabolites in the state of frenzy energy is Lactate, which is expected to be up-regulated and in higher concentrations in the M1 active state, according to the above mentioned references.

Although there are some studies with results that do not follow the main stream. For example in the work of Hollenbaugh and collaborators (*56*) they used a macrophage model (although not macrophages derived from human primary monocytes; *i.e*. U1 and U937 cells), and found significant reductions in the levels of some glycolytic intermediates such as hexose-P, FBP, and G3P, coupled with a decrease in glucose uptake, suggesting a down-regulation or suppression of glycolysis in HIV infected macrophages. However, they found an increase in the levels of pyruvate, suggesting that either this comes as an effect of a down-regulation of the TCA cycle, or is a *de novo* synthesis of pyruvate through other sources (amino acid oxidation). Although it does not exactly follow the model of the Warburg effect in M1 macrophages, or the TCA cycle in M2 macrophages (*12*), the different source of cells has to be taken in account, and the use of another type of virus (HIV).

Dendritic cells (DC) play a key role within both branches of the immune system (*57*), especially by capturing antigens and presenting them to T-cells of the adaptive immune system (*58,59*). Malinarich *et al*. (*60*) (Table 2) evaluated the different metabolic profiles of monocyte derived DC (moDC) in several differentiation stages. After an analysis of the differentially expressed genes (DEGs) and their functional annotation enrichment, they observed a distinct profile in immature or tolerized moDCs against mature moDCs. Importantly, they have described that there is a OXPHOS activity decrease with immunogenicity, which is highest in mature moDCs, as indicated in the review by Kelly and O'Neill (*28*) (Table 2).

Natural Killer (NK) cells are another set of important players for the immune system (*61,62*), belonging to the innate immune branch. Among their functions NKs kill infected cells after recognition (*63*), for example those infected by virus without prior immunization (*64*). Metabolism of this type of cells has been also described, where the mammalian target of rapamycin (mTOR) (*65*) plays a significant and central role for their activation (*66*) (Table 2). It has been shown recently that their anti-viral activity is severely affected by hypoxia (*64*), a situation that can in general disturb the first stage of the TCA cycle (*67*). Murine NK cells have been reported to display a rather metabolically inactive state prior to activation, and no significant increase in glycolysis or OXPHOS after short-term activation (*68*) (Table 2), changing into an increased overall metabolism and especially glycolysis after high-dose prolonged culture with IL15. Additionally, the external environment is capable of influencing NKs, as dietary high-fat intake has also been related to a decrease in the cytotoxicity of NK cells (*69*). In keeping with those results, Viel *et al*. (*70*) have shown that NK cells in obese subjects were less responsive to stimulation, and that could lead to a higher susceptibility to viral infections in this study group. Lastly, it has been addressed that during bacterial infections in acute phases there is a subchronic inflammation state that leads to insulin resistance (*71*). That has the effect of more available energy for the immune system (synthesis of glucose, increased circulating levels of glucose) for fuelling the immune system, in keeping with the reported observations of the Warburg effect in some immune cell lines. Interestingly enough, this subchronic inflammation state is similar to what has been reported in obesity studies (*72,73*), and as reviewed here has a direct impact on the phenotype of NK cells.

4. Conclusion and research directions

It is clear that there is a metabolic component of the immune system that is important for the immune response, involving cells of innate immunity, and that these cells (among others) can shift their activities depending on the conditions in the human body, *e.g*. a viral infection. Viruses can as well modify the metabolic state of the cells, due to their synthetic genome, especially those with really small and reduced ones. Metabolomics is a useful approach to systematically and quantitatively study viral cellular regulation and control, through the screening of

metabolites, through the use of Gas Chromatography-Mass Spectrometry (GC-MS) or Nuclear Magnetic Resonance (NMR) among other platforms. It is also very interesting to profile metabolites, as they are the end point of the interaction between genes, transcripts and proteins, a reflection of the phenotype of a cell or given organism (*74*). Nevertheless, a main complication in metabolomics analyses is the variation that can be observed among individuals (*27,75*). Although a global perspective could be sought, comparing healthy individuals and infected patients, the expected variation emerging from several cell lines present in the body and response to the infection in a systemic way, would increase the difficulty in the analysis. A more concrete study would be to restrict this metabolite profiling to single cell lines, because this approach would decrease variability.

Metabolism is also an important part of the innate immune system, and there is an overall association of immunogenic phenotypes with an increased rate in OXPHOS. Importantly, the metabolic state of the organism has a direct impact over the function of immune cells, such as NK cells. Obesity has been shown to impair their functions, and could be an explanation for higher susceptibility to viral infections in obese subjects. It is interesting to try to address if metabolism is an alternative pathway for the recognition of pathogens, in another level of innate immunity.

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