Mini Review

Impact of Viruses on Host Metabolism

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Abstract | Viruses are obligate intracellular pathogens and rely on host machinery to successfully cause infections. In order to succumb hosts, viruses have evolved strategies to manipulate specific cellular metabolic pathways that aid the production of viral particles. Viruses need to breach a complex network of metabolic intrinsic factors and microenvironment established within the host cells. The pressure exerted by invading pathogen disrupts the internal balance and dictate the host-pathogen niches. For absolute survival, proliferation, and propagation inside the host cell, viruses modulate certain metabolic pathways to destabilize the host metabolism. These alterations in host metabolic signaling as a result of virus-host interaction generate a favorable environment for the viral pathogens. This phenomenon is a hotspot for investigations in order to improve the diagnosis and drug development of future antiviral therapeutics. In fact, metabolism is considered as a crucial player in the cascade of viral interactions, its modulation is essential to decide the final outcome of viral infection. Here, we concisely present how viruses alter the metabolic pathways for their own survival.

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Introduction

With the inception of metabolomics, scientists are able to undermine the metabolic insights of host-pathogen interaction. Investigators are still striving to find the key solutions on how viral pathogens are capable to utilize cellular machinery of the host for their own survival. Viruses, as intracellular parasites, hijack the cellular metabolic pathways to manifest their pathogenic nature (Bardell and Essex, 1974; Singh, Singh, August, and Horecker, 1974). It is firmly considered that most of the viruses induce catabolism and an increase in nutrient uptake to facilitate the production of the viroid particles (Levene and Gaglia, 2018). The cascade of replication and packaging of viral particles require an ample amount of energy in the form of adenosine triphosphate (ATP). Earlier in the 1960s, scientists started to investigate the impact of viruses on host metabolism. Previously, it was established that viruses manipulate carbohydrate metabolism (Levy and Baron, 1957). However, more recent studies throw light on the cellular and molecular basis of viral-cell metabolic interaction. Additionally, sincere efforts have been made to undermine the possible impact of viral-induced metabolic alterations in the manifestation of viral diseases. Therefore, it is mandatory to deeply study the virus-induced metabolic modifications for the development of novel antiviral drugs and therapeutics.

How viruses breach carbohydrate metabolism

During normal conditions, oxidation of glucose is the chief source of providing nutrition and energy to the cells. In anaerobic conditions, glucose is metabolized

into pyruvate, which upon translocation to the cellular organelles (mitochondria), catabolized into tricarboxylic acid (TCA) cycle and further recruited to electron transport chain (ETC) to generate energy packets in terms of ATP. However, in the hypoxic scenario, where a huge amount of energy is required, energy is rapidly generated by directing glucose into lactic acid fermentation. Viruses, as the obligate cellular pathogen breach this carbohydrate metabolic pathway. In the 1950s, two scientists, for the first time revealed that poliovirus requires glucose for their propagation where viral growth was stopped in the absence of glucose in HeLa cells. Interestingly, glucose supplementation again resulted in normal viral propagation (Eagle and Habel, 1956). Strikingly, in case of human immunodeficiency virus (HIV), severe metabolic depletion of glucose appears in T cells that was due to the fact that HIV mainly targets cluster of differentiation (CD4) T cells (Buck, O'sullivan, and Pearce, 2015). Upon viral attachment to T cell receptors (TCR), co-stimulation of CD28 is mainly required to maximize the glucose influx by overexpression of glucose transporter (GLUT) 1 (Jacobs et al., 2008). In homeostatic conditions, viral reverse transcription is stopped. However, once the T-cells get activated, viral reverse transcription initiates leading to the formation of new progeny (Bukrinsky, Stanwick, Dempsey and Stevenson, 1991; Chun et al., 1997). In this scenario, overexpression of GLUT1 and associated glucose intake is mandatory for the establishment of HIV infection (Loisel-Meyer et al., 2012; Palmer et al., 2014).

Similarly, T helper cells (Th17) are mainly associated with two essential biological entities that regulate glucose metabolism including hypoxia-inducible factor 1 alpha (HIF-1α) and chemokine receptors (CCR6) (Shi et al., 2011). Furthermore, it is postulated that Th17 is a central reservoir to contain HIV (Gosselin et al., 2017). Recently, a study demonstrated that HIV infected patients demonstrated the depletion in circulating CD4 T cells establishing reduced GLUT1 expression on CD4 cells (Palmer et al., 2014). This phenomenon can be associated with immune functionality in virus-mediated infection. Additionally, studies have demonstrated that lymph nodes in the gastrointestinal tract including (ileocecal, mesenteric, splenic lymph nodes) are the primary sites for glucose metabolism in viral infection and hence, presented as the major sites of viral propagation (Cumont et al., 2007; Santangelo et al., 2015). Similar to CD4 T cells, macrophages are the potential cells in innate immune response, that are capable of viral clearance by phagocytosis (Laforge et al., 2011). Viruses like HIV, impacts on macrophages by overexpressing glycolytic enzymes including pyruvate kinases muscle type 2 (PKM2) and hexokinase (HK) (Barrero et al., 2013). Then, the enhanced influx of glucose results in the establishment of a favorable environment for viral manipulation and survival within the macrophages. This is truly in agreement with the previously published literature demonstrating how viruses utilize glycolytic metabolism for their survival.

Similar to HIV, numerous other viral pathogens hijack the cellular machinery of the host for their own survival. One such example is the Human herpesvirus (HHV)-8, also termed as Kaposi's sarcoma-associated herpesvirus (KSHV) (Delgado et al., 2010). As a gamma herpes virus, it has the key potential to infect a variety of cells including dendritic cells, monocytes, and epithelial cells of oral and endothelial mucosa (Ye et al., 2016). It is believed that in order to maintain its progeny, HHV-8 creates latency in the cell by mere shifting cellular metabolism towards fermentation (Yogev, Lagos, Enver and Boshoff, 2014). In this way, this virus is capable of creating viral particles leading to successful viral infection. Recently, it is established that the hyperglycemic environment is mandatory for the activation of HHV-8. Fascinatingly, elevated levels of phosphorylation for the key mediators in glucose metabolism, named as AKT and GLUT1 resulted in response to HHV-8 infection in THP-1 cells (Gonnella et al., 2013).

The Epstein-Barr virus (EBV), a crucial virus in the cohort of mammalian viruses, demonstrates the expression of HIF1-α in response to a potent viral oncoprotein, the latent membrane protein 1 (LMP1). The overall cascade involved in EBV propagation is the overexpression of HIF1-α under the influence of mitogen-activated protein kinase (MAPK), and the production of hydrogen peroxide, elevated vascular growth factors (VEGF), that finally resulted in angiogenesis and invasiveness (Wakisaka et al., 2004). Similar to HHV-8, adenoviruses also mimics the Warburg effect, whereupon viral infection, the rate of glycolysis in epithelial cells dramatically elevates (Wakisaka et al., 2004). This is due to the overexpression of MYC, a proto-oncogene in its nature.

All adenoviruses utilize E4ORF1, a viral polypeptide,

to express MYC for their optimal propagation and survival (Thai et al., 2014).

Dengue virus (DENV) belongs to *Flaviviridae*, as a hemorrhagic viral pathogen of humans, also manifests glycolytic alterations. The mechanism of glucose uptake was amazingly modified by DENV, where several glycolytic metabolites were up taken at various intervals of viral propagation (Fontaine, Sanchez, Camarda and Lagunoff, 2015). Similarly, Zika virus alters the GLUT1 functionality by stopping normal glucose influx in the endothelial cells (Blonz, 2016). Thus the growth and development of the fetus are markedly affected. Furthermore, comprehensive studies are mandatory to elaborate on the glycolytic imbalance caused by the Zika virus in the host cells.

Glucose influx is integral to fulfill the bioenergetics of the host cellular machinery. Viruses breach this metabolic cascade in the host cell for their own proliferation and survival. Additionally, the elevated level of glucose in virus-infected cells further delineate the nutrition requirement of viral pathogens. The viral induced alterations and modifications in the host cell are mandatory for the establishment of successful viral infection by the invading pathogen. However, key contributors and fundamental modulators involved in the cascade of viral-mediated carbohydrate metabolism need further elaboration. Further investigations will bring new horizons to develop novel antiviral therapeutics for a better clinical outcome.

The role of viruses in lipid metabolism

As a key contributor in cell membrane integrity, cellular proliferation and metabolism, lipids as fatty acids (FAs), are the macromolecules that are served as the source of energy within a cell. In the cell, these FAs are stored in the form of triglycerides. The synthesis of FAs takes place in the cytosol, whereas, upon lipase degradation, FAs enter into the mitochondria where, under the influence of oxidative degradation, Acetyl-CoA is the end product. The crucial role of fatty acids in virus-associated infections is deeply undermined and broadly screened to understand the key mechanisms associated with lipid degradation in virus-infected cells. These lipids are chiefly involved in the viral life cycle where they are an integral part of mechanisms including endocytosis, host-cell signaling, bio-energetics, and viral progeny.

Lipids in the host's cellular membranes, serve as the first barrier against viral infections. However, like other metabolic pathways, viruses exploit this mechanism for their successful attachment and entry into the host cell. Lipids are chiefly responsible for maintaining membrane fluidity and integrity of the cells. Some viruses interact with the host cells by attaching the viral envelope with the external cellular membrane, while in some instances, invading viruses directly interact with the plasma membrane for successful adhesion.

In order to establish a successful virus-cell interaction, viruses have evolved certain key regulators that serve as essential tools for their propagation. One such example is the use of gangliosides as specialized receptors by members of polyomavirus family, murine polyomavirus and simian virus 40 (SV40) (Qian and Tsai, 2010; Tsai et al., 2003). Fascinatingly, it was revealed that on one side ganglioside GD1a establishes successful binding of the virus to the host membrane while on the other side its glycoprotein subunit prevents its entry in the endoplasmic reticulum. Another contrasting feature is the presence of glycosphingolipids in the outer surface of HIV, it is established that it aids the viral entry into the dendritic cells (Izquierdo-Useros et al., 2012).

Virions of the *Filoviridae* and *Flaviviridae*, such as Ebola virus, dengue virus and West Nile possess specialized biological entities phosphatidylethanolamine that upon interaction with phosphatidylserine (PS) receptors allow viral invasion (Richard et al., 2015). However, viruses of the *Flaviviridae* including HCV demonstrated attachment with low-density lipoproteins (LDL) receptors, whereas, DENV achieve viral binding with very low-density lipoproteins via specialized capsid proteins present on their surface (Agnello, Ábel, Elfahal, Knight and Zhang, 1999; Faustino et al., 2014; Molina et al., 2007).

Viruses such as Marburg and Ebola integrate highly specialized raft-associated moieties, which are believed to be involved in the viral outflow (Bavari et al., 2002). A highly specialized protein Niemann-Pick C1 (NPC1) is considered as crucial in filovirus infection. Studies have established that a decrease in cholesterol levels manifests a remarkable decline in viral infection which was eliminated after exogenous successive cholesterol treatment (Carette et al., 2011).

Viral particles including, influenza A and respiratory

syncytial virus (RSV) contain a sufficient amount of cholesterol as an integral component of their viral envelope which provides stability to the virion (Bajimaya, Frankl, Hayashi and Takimoto, 2017). However, the depletion of cellular cholesterol resulted in malfunctions in viral budding and release from the host cell. It was significantly observed that cholesterol-reducing drugs caused significant variability in new viral progeny. Likewise, exogenous cholesterol supplementation resulted in both virion infectivity and stability. Similarly, the same pattern of infectivity (impaired viral release) was observed in human parainfluenza type 1 and Sendai virus (SeV) (Bajimaya Hayashi et al., 2017).

Invading viral pathogens significantly alter the host cellular metabolism for their integrity and survival. The key strategies by which viruses breach lipid signaling have been deeply studied in terms of viral infections. However, a more comprehensive approach is mandatory to delineate the cellular and molecular basis of virus-host interaction. This insight will be advantageous for future drug designing to prevent and control these viral ailments.

Viral impact on proteolysis

Amino acids play a central role in cellular metabolic pathways. Glutamine, as a nonessential amino acid, actively breaks down into α-ketoglutarate (αKG) via enzymatic activity of glutamate dehydrogenase. Once αKG enters into mitochondria, it has the ability to replace the TCA cycle, hence allowing its activity. It is also an integral part of two fundamental cellular processes, the synthesis of purine and glutathione. Although glycolysis is considered as the pivotal metabolic pathway with which energy is supplemented in viral infections, other metabolic systems also prevail and actively stolen by the invading pathogens. One such example is glutaminolysis.

It was presented that glutamine, along with glucose, is mandatory for the optimum viral propagation of poliovirus (Eagle and Habel, 1956). Furthermore, experimentation revealed that in the absence of glutamine in the cell culture media, viral replication sustained (Darnell Jr. and Eagle, 1958). Strikingly, it was also established that an increase in viral replication was seen when supplemented with glutamine in the media, suggesting that glutaminolysis is a crucial metabolic pathway in viral propagation (McKeehan, 1982).

Members of the *herpeseviridae,* including human cytomegalovirus (HCMV) and herpes simplex-1 (HSV-1), both employ a unique mechanism for their propagation where they enhance pyruvate carboxylation (Vastag, Koyuncu, Grady, Shenk and Rabinowitz, 2011). Increased uptake of glutamine and ammonia by HCMV-infected fibroblasts further augmented the statement of glutamine supplementation and glutaminolysis by virions. Similarly, another viral pathogen that poses great economic losses in fisheries is the infectious spleen and kidney necrosis virus (ISKNV). Studies demonstrated that variations in glutamine degradation were observed in ISKNV-treated cells (Fu et al., 2017). Strikingly, vaccinia virus is peculiar in terms of glutamine uptake for its appropriate replication. In the absence of glutamine, the less viral progeny was observed, while glutamine supplementation dramatically enhanced the viral progeny (Fontaine et al., 2015). In HIV, a similar phenomenon was observed where virus-infected macrophages demonstrate significant alterations in glutaminolysis. Additionally, it was also established that elevated level in glutamine release was seen, under the influence of Vpr (a viral protein) in HIV-mediated nervous disorders (NeuroAIDS) (Datta et al., 2016).

These findings present a therapeutic advantage that glutamine metabolism can be targeted during viral infection to limit the viral load. It can be anticipated that virus-induced glutaminolysis is mandatory for survival, propagation, and replication of certain viral particles. However, broad investigations need to be conducted in order to elucidate if glutaminolysis is only meant for energy generation or also contribute to viral propagation.

Conclusion and Recommendations

Outstanding advancements in the domain of metabolomics have been made in recent years that allowed investigators to deeply undermine the cellular processes. The advancement in cutting-edge practices further aid to intensely comprehend the complex integrated and interconnected virus-induced metabolic pathways. Viruses, as an obligate intracellular parasite, possess the peculiarity to hijack the cellular machinery of the host. However, to comprehensively investigate the mode of virus-mediated metabolic dysfunction in host cells is still a challenge.

Several queries need to be addressed including the

possible route of virus-induced metabolic signaling, the impact of these modifications in metabolic signaling and the final outcome of the infection. Moreover, this metabolic distress can further produce sequelae of viral infections.

More precise and pinpoint targeting of metabolic pathways is a fundamental step to forecast the possible antiviral targets. However, viruses are distinct and complex in their actions as they induce diverse energetic and metabolic needs in their host. These facts necessitate inclusive and deeper investigations targeting the impact of host-cell metabolism in a particular viral infection. Studies associated with antiviral potential, innate immune responses, cell bioenergetics, apoptosis, and immune signaling are mandatory to further delineate the metabolic webs. This will bring a new horizon in drug discovery and therapeutic designing against viral invaders.

Author's Contribution

Conception and writing of the manuscript: MA, re-structuring and improvement by YX

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