Contemporary Strategies and Current Trends in Designing Antiviral Drugs against Dengue Fever via Targeting Host-Based Approaches

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Dengue virus (DENV) is an arboviral human pathogen transmitted through mosquito bite that infects an estimated ~400 million humans (~5% of the global population) annually. To date, no specific therapeutics have been developed that can prevent or treat infections resulting from this pathogen. DENV utilizes numerous host molecules and factors for transcribing the single-stranded ~11 kb positive-sense RNA genome. For example, the glycosylation machinery of the host is required for viral particles to assemble in the endoplasmic reticulum. Since a variety of host factors seem to be utilized by the pathogens, targeting these factors may result in DENV inhibitors, and will play an important role in attenuating the rapid emergence of other flaviviruses. Many experimental studies have yielded findings indicating that host factors facilitate infection, indicating that the focus should be given to targeting the processes contributing to pathogenesis along with many other immune responses. Here, we provide an extensive literature review in order to elucidate the progress made in the development of host-based approaches for DENV viral infections, focusing on host cellular mechanisms and factors responsible for viral replication, aiming to aid the potential development of host-dependent antiviral therapeutics.

The host’s cellular metabolism provides the necessary energy (ATP), biosynthetic building blocks, and other important molecules required for viral replication. In DENV infection, a major change occurs in the central carbon metabolism, especially in glycolysis, whereby the expression of both glucose transporter I (GLUT1) and hexokinase II (HK-II) is up-regulated and glucose consumption is increased in DENV-infected cells. DENV activates the glycolytic pathway for viral metabolic requirements and life cycles, including energy, replication, and biosynthetic building blocks [60]. Glucose and glutamine serve as the main carbon sources in healthy cells and the tricarboxylic acid (TCA) cycle generates ATP using the oxidation of glucose via glycolysis. However, in some cases, glutamine serves as an ATP generator in the TCA cycle instead of glucose, so that it can be utilized for biosynthetic processes (Figure 2), such as in the case cancer cells and human cytomegalovirus (HCMV) cells [3–6]. As DENV activates the host glycolytic pathway for generating their necessary building blocks, pharmacologic regulation of glycolysis significantly blocks infectious DENV production. Krystal and colleagues reported that glycolysis inhibition through sodium oxamate and 2-deoxy-d-glucose (2DG) treatment can result in a significant reduction in DENV replication [5].

References

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Keywords

Dengue virus; Glycolysis for Dengue virus; Metabolic pathways for Dengue virus; Dengue antiviral drug; Dengue Host target

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