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The role of lipid metabolism in antiviral drug targeting.

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Introduction

Lipid metabolism plays a central role in maintaining cellular integrity, energy balance, and signaling. In the context of viral infections, lipids are more than structural components—they are active participants in the viral life cycle. Viruses exploit host lipid pathways for entry, replication, assembly, and egress. This dependency has opened new avenues for antiviral drug development, where targeting lipid metabolism offers a promising strategy to disrupt viral propagation. As emerging and re-emerging viruses continue to challenge global health, understanding the interplay between lipid metabolism and viral mechanisms is critical for therapeutic innovation [1].

The initial step in viral infection—entry into the host cell—is often mediated by interactions with lipid-rich domains in the plasma membrane. These domains, known as lipid rafts, are enriched in cholesterol, sphingolipids, and glycolipids, and serve as platforms for receptor clustering and membrane fusion. For example, SARS-CoV-2 utilizes its spike protein to bind to the ACE2 receptor, a process facilitated by cholesterol and ceramide-enriched microdomains. Linoleic acid, a polyunsaturated fatty acid, stabilizes the spike protein's receptor-binding domain, modulating its accessibility to ACE21. Disrupting these lipid interactions can hinder viral entry, making lipid rafts attractive targets for antiviral intervention [2].

Once inside the host cell, many viruses hijack lipid metabolism to create replication organelles. Lipid droplets (LDs), which store neutral lipids like triacylglycerides and cholesterol esters, are repurposed by viruses as replication hubs. Coronaviruses, flaviviruses, and hepatitis C virus (HCV) are known to induce LD biogenesis to support viral RNA synthesis and protein assembly. Fatty acid synthesis and cholesterol esterification are upregulated during infection, providing the necessary lipid scaffolds. Inhibiting these pathways can impair viral replication, as demonstrated by the antiviral effects of fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) inhibitors [3].

Lipids also influence host immune responses. Oxidized cholesterol derivatives, such as oxysterols, modulate inflammation and antiviral signaling. Some viruses manipulate lipid metabolism to suppress immune detection—for instance, by altering sphingolipid levels to inhibit interferon responses. Targeting lipid-mediated immune evasion can enhance antiviral immunity. Statins, commonly used to lower cholesterol, have shown immunomodulatory effects that may benefit viral clearance. Moreover, acid sphingomyelinase (ASM) inhibitors reduce ceramide levels, disrupting viral entry and promoting immune activation [4].

Several FDA-approved drugs that modulate lipid metabolism are being repurposed for antiviral therapy: Beyond lipid-lowering, statins exhibit anti-inflammatory and antiviral properties. They interfere with cholesterol-dependent viral entry and reduce cytokine storms in severe infections. Drugs like amitriptyline and fluoxetine inhibit ASM, reducing ceramide-mediated viral fusion. Targeting fatty acid synthesis impairs the formation of replication organelles, limiting viral propagation. Fingolimod, used in multiple sclerosis, modulates sphingolipid signaling and may have antiviral potential. These agents offer dual benefits—disrupting viral life cycles and modulating host responses—making them attractive candidates for broad-spectrum antivirals. Advances in lipidomics have enabled detailed profiling of lipid alterations during viral infections. By identifying lipid signatures associated with viral replication and pathogenesis, researchers can pinpoint metabolic vulnerabilities. For instance, lipidomic studies in

COVID-19 patients revealed elevated levels of ceramides and altered cholesterol metabolism, correlating with disease severity. Such insights guide the development of targeted therapies and biomarkers for treatment response [5].

Conclusion

Lipid metabolism is intricately linked to the viral life cycle, influencing entry, replication, assembly, and immune evasion. Lipid pathways are essential for normal cellular function. Broad inhibition may lead to off-target effects and toxicity. Different viruses exploit lipid metabolism in distinct ways. A one-size-fits-all approach may not be feasible. Viruses may adapt to lipid-targeting drugs by rerouting metabolic pathways or mutating lipid-interacting proteins. To overcome these hurdles, combination therapies and precision medicine approaches are being explored, tailoring interventions to specific viral and host profiles. The integration of lipidomics, systems biology, and artificial intelligence is accelerating antiviral drug discovery. Future strategies may include: Identifying patient-specific lipid alterations to guide therapy. By targeting lipid pathways, researchers can disrupt viral propagation and enhance host defenses. While challenges remain, the strategic modulation of lipid metabolism offers a promising avenue for antiviral drug development. As emerging viruses continue to pose global threats, lipid-targeting therapies may become essential tools in our antiviral arsenal.

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