Towards a Breakthrough in HSV-1 Treatment: Targeting Key Proteins To Halt Viral Propagation

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Herpes Simplex Virus-1 (HSV-1) infects around 70% of the global population, causing cold sores on the lips and genitals. This study presents a novel antiviral approach targeting plakin proteins, essential for cell migration, cytoskeletal organization, and viral transport. Viruses exploit plakins like MACF1 and BPAG1 to facilitate their intracellular movement and replication. Prior studies showed that silencing BPAG1 impairs HSV-1 infection and that viral tegument proteins interact with BPAG1 to enable viral egress via microtubules. MACF1 also links actin fibers and microtubules, aiding intracellular trafficking. To evaluate the therapeutic potential of targeting these proteins, Vero cells were treated with Ibrutinib and Tacrolimus, two FDA-approved drugs known to bind to the pockets of these proteins. Though used for cancer and immunosuppression, these compounds may also modulate intracellular transport pathways exploited by HSV-1. MTT assays confirmed no cytotoxicity at experimental concentrations. Antiviral effects were assessed using fluorescence microscopy, plaque assays, western blotting, and confocal microscopy. In a precedent-setting result, post-infection treatment with Ibrutinib (50 µM, MOI:1) inhibited 99.63% of viral replication. Remarkably, pre-treatment with Ibrutinib also exhibited significant inhibition, suggesting vaccine-like preventive properties. Tacrolimus, in contrast, showed minimal antiviral effect. These findings support that Ibrutinib inhibits HSV-1 by targeting plakin-dependent microtubule functions. Additionally, viral capsids were observed accumulating at centrosomes, reinforcing the role of microtubule networks in HSV-1 transport. As all herpesviruses rely on microtubules, this approach may be broadly applicable beyond HSV-1.

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