How Do EBV, HPV and HIV Converge on the USP7–MDM2–p53 Axis to Promote Oncogenesis?

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Abstract:

The USP7-MDM2-p53 pathway is a crucial tumour-suppressive mechanism that multiple oncogenic viruses exploit to evade the host immune system. Emerging evidence shows that multiple oncogenic viruses, including Epstein–Barr virus (EBV), human papillomavirus (HPV), and human immunodeficiency virus (HIV), exploit this pathway to subvert host tumour defences and promote oncogenesis. This review synthesises current understanding of how each virus interacts with the USP7–MDM2–p53 network, including EBV's use of EBNA1 to sequester USP7, HPV E6/E7-driven p53 degradation and stabilisation of viral oncoproteins, and HIV Tat/Nef-mediated suppression of p53 via MDM2 stabilisation. Although differing taxonomically and mechanistically, these viruses that inactivate p53 converge on USP7 as one of the regulatory fulcrums. By locating this convergence, we have identified USP7 as a common target with translational potential. Targeting USP7 with small-molecule inhibitors or CRISPR-based approaches holds promise but poses challenges due to concerns over specificity and toxicity, making it a promising yet complex approach for antiviral and anticancer strategies. This review is the first to synthesise evidence that EBV, HPV, and HIV converge on USP7 as a shared regulatory hub, despite their taxonomic and mechanistic differences. Targeting USP7 presents a promising but complex therapeutic strategy, warranting further research into virus-specific inhibitors and combinatorial approaches.

Keywords:

p53, USP7, MDM2, Viral oncogenesis.