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Screening of novel inhibitors targeting Human Papillomavirus 16 E6/AP/P53 ternary complex towards development of therapeutic strategies against HPV-mediated oncogenesis

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Abstract

Cervical cancer is the fourth most common cancer in women worldwide. It is well known that high-risk HPV is the main etiological agent for this infectious viral carcinoma. Human papillomaviruses are small (50 nm) double-stranded DNA viruses composed of a genome of 8 kilobase pair, enclosed inside a non-enveloped capsid protein. The genome includes three portions: (a) early genes (E1, E2, E4, E5, E6, E7) those regulate the vegetative and productive phase of viral life cycle; (b) late genes (L1, L2) which encode the capsid protein and (c) a noncoding regulatory region called long control region (LCR) involved in the regulation of viral replication and transcription. The HPV oncoproteins E6 and E7 recognize numerous host proteins, in large part by hijacking cellular domain-motif interaction networks. E6 and E7 oncoproteins disrupt cell cycle checkpoint control by inhibiting CDKs inhibitors (P21, P27) and degrading P53. In the process of E6 mediated degradation, E6 binds to a short leucine (L)-rich LxxLL consensus sequence within the cellular ubiquitin ligase E6AP3. Subsequently, the E6/E6AP heterodimer recruits and degrades p53. The LxxLL peptide of E6AP is sufficient to render E6 liable to interact with p53 'core' (DNA binding) domain of p53 required for the interaction with E6/E6AP9–11. In the present study, we explored specific novel inhibitors targeting three different druggable pocket i.e., E6-binding cleft, LxxLL pocket of AP and the p53-binding cleft of E6/E6AP/p53 ternary complex using AutoDock tool. A total of five novel compounds with higher binding energy were identified as potential competitive inhibitors against HPV16 E6/AP/P53 ternary complex. The combinatorial strategies targeting these druggable pockets are expected to open up better avenues for the development of therapeutic strategies against HPV-mediated oncogenesis in near future.

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