Computer aided drug design for developing potential inhibitors of oncogene PELP1 for treating breast cancer

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Abstract

Most patients with estrogen receptor alpha-positive breast cancers (ER+ BC) initially respond to treatment but eventually develop therapy resistance with disease progression. Overexpression of oncogenic ER coregulators, including proline, glutamic acid, and leucine-rich protein 1 (PELP1), are implicated in BC progression. The lack of small molecules that inhibits PELP1 represents a major knowledge gap. Here, using a yeast-two-hybrid screen, we identified novel peptide inhibitors of PELP1 (PIPs). Biochemical assays demonstrated that one of these peptides, PIP1, directly interacted with PELP1 to block PELP1 oncogenic functions. Computational modeling of PIP1 revealed key residues contributing to its activity and facilitated the development of a small molecule inhibitor of PELP1, SMIP34, and further analyses confirmed that SMIP34 directly bound to PELP1. In BC cells, SMIP34 reduced cell growth in a PELP1-dependent manner. SMIP34 inhibited proliferation of not only wild-type (WT) but also mutant (MT) ER+ and therapy-resistant (TR) BC cells, in part by inducing PELP1 degradation via the proteasome pathway. RNA-seq analyses showed that SMIP34 treatment altered the expression of genes associated with estrogen response, cell cycle, and apoptosis pathways. In cell line-derived and patient-derived xenografts of both WT- and MT- ER+ BC models, SMIP34 reduced proliferation and significantly suppressed tumor progression. Collectively, these results demonstrate SMIP34 as a first-in-class inhibitor of oncogenic PELP1 signaling in advanced BC.