A flexible-docking approach for the design of novel cancer peptidomimetic drugs

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Abstract

Cancer is the second leading cause of death worldwide and the lack of alternative therapies has kept patients dependent on classic chemotherapy. The most occurring form of cancer amongst women is breast cancer and the triple negative cell subtype (TNBC) is responsible for a high metastatic and mortality rate, as it presents molecular and genetic shifts, lacks specific targeting and responds poorly to existing therapies. Recent studies have provided convincing evidence that the therapeutic outcome of chemotherapy may be affected by the expression and activity of receptor tyrosine kinases and their phosphatase pathways (MAPK/ERK, PI3/AKT, among others). These proteins are implicated in mechanisms of cell survival, drug resistance and Epithelial-Mesenchymal Transition (EMT), and are therefore key targets for TNBC cancer cell subtype. However, many inhibitors developed for these targets have not succeeded at a clinical level and present low solubility.

As a result of the pronounced decline in productivity experienced by drug discovery efforts in the last years, novel approaches to the rational design of new drugs are now being pursued. A potential solution might be the use of natural or synthetic peptides and peptidomimetics targeting protein-protein interactions essential for signaling networks function. The combination of several bioinformatic approaches (docking, virtual screening, pharmacophore models, among others) allows the use of the vast amount of existing information on available compounds and protein-protein interactions in structural databases.

In this study we designed a procedure for small peptidomimetics structure-based rational drug design capable of blocking the active sites of SNAiL1, a protein that has been suggested as a potent repressor of E-cadherin expression and consequently, as an inducer of EMT transition in TNBCs. A random library was created using a composite approach for drug-like compound identification from the PubChem and Development Therapeutics NCI/NIH compound databases, which combined structure-based virtual screening (known motifs of peptide structures within proteins and small molecules) and Z-score comparison. Docking studies were performed to map the polypeptides activity and stability: (1) point alteration studies using non-natural aminoacids for helical stability over a wider range (since linear peptides adopt many confirmations in aqueous solution) using Ramachandran plot dihedral angles estimation; (2) quantitative structure-activity relationships (QSAR) using radical modification chemical studies and (3) umbrella sampling for dissociations studies. The peptidomimetic SNAiL1 model created suggested at least two radical modifications for a strong inhibition.

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