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Engineering of bovine pancreatic ribonuclease to induce apoptosis in cancer cells

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Abstract

Ribonucleases (RNase) are responsible for the degradation of RNA. RNase are a superfamily of enzymes which catalyze the degradation of RNA into smaller components. These enzymes can be potentially cytotoxic because they can inhibit protein synthesis and induce apoptosis, thus RNase could be considered as a potential candidate for cancer chemotherapeutic. Ribonuclease inhibitor (RI) is a cytosolic protein that binds to pancreatic-type ribonucleases with femtomolar affinity and renders them inactive. In this research the bovine pancreatic ribonuclease A (RNase A) was used to design an engineered enzyme with the lowest affinity to cytosolic RI. Nucleotide and amino acid sequences of RNase A and RI were obtained from the protein data bank (PDB) and UniProt databases. In order to engineer the enzyme, the candidate amino acids in the native RNase A, which play a role in binding to RI, were selected and replaced on basis of size without changing in spatial form. For comparison of affinity between native and engineering enzymes with RI, molecular docking was conducted by online Hex and ClusPro 2.0 web servers. The obtained results from 3D modeling and molecular docking showed that alteration of Lys7, Arg39, Asp67, Asp71, Gly88, and Glu111 did not have any effects on structure of RNase A, and reduced affinity between RNase A and RI. This finding will need experimental validation and can be useful in the development of a new class of chemotherapeutics agents based on pancreatic ribonucleases.

Keywords: Cell and Cancer, Cancer Genetics, Cancer Treatment and Management, Targeted Cancer Therapy, Drugs and Cancer

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