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Engineering of ovine pancreatic Ribonuclease for increasing of cytotoxicity activity: an *in silico* approach

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Abstract: The *death rate* from *cancer* has declined steadily over the past 2 decades worldwide. Conventional methods such as surgery with chemotherapy and/or radiation have a number of unwanted impacts on patients. Therefore, design of new generations of drugs like immnutoxins which may have fewer side effects is necessary. Ribonucleases are a large group of hydrolytic enzymes that degrade ribonucleic acid (RNA) molecules [1]. They can be cytotoxic as well, since the cleavage of RNA renders its information illegible, thus RNase could be considered as a potential candidate for cancer chemotherapeutic. Ovine pancreatic ribonuclease enzyme is a member of super family RNase A but this enzyme is inhibited by RNase inhibitor after internalizing to the cell. The objective of this research was to engineer RNase A by substitute amino acid sequences for evading of RNase inhibitor or reducing affinity of RNase A to RNase inhibitor. Substitutions must be chosen carefully to minimize deleterious effects on either catalytic activity or conformational stability [2]. In addition, positive charge manifested either as a high net molecular charge (Z) or in discrete regions of cationicity, is crucial for the favorable Coulombic interactions with anionic components of the cell surface. 3D structures were drawn by SWISS-MODEL. 3D alignments of native RNase A and modified RNase A were assessed by SWISS-MODEL. Docking of RNase A and RI was evaluated using ClusPro 2.0 on-line application. Amino acid sequences of wild- type RNase A and RI retrieved from the NCBI GenBank. Six amino acids were subjected to substitution which were including (lysin7, arginine39 and …). This investigation based on docking analysis showed that substituted amino acids did not have any effect on structure on RNase A, thus its activity was preserved. Also interaction between mutant RNase A with RI revealed that mutant RNase A can evade RI while docking of native RNase A with RI, showed that native RNase A was totally inhibited by RI. Finally, this *in silico* study suggest that the cytotoxic activity of RNase A may be increased using these amino acid substitutions and this could be further studied to design new drugs against cancer cells.

Key words: Immnutoxins; RNase pancreatic; RNase inhibitor; cancer

References

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