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Accounting of the influence of point mutations of BH3-peptide on the stability of the formed biological complex on the example of the Bcl-2 family proteins

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This report presents a new method that allows one to qualitatively determine the effect of point mutations in peptides on the stability of the formed complex with full-length proteins. On the basis of the developed approach, a qualitative correlation of the obtained results with the dissociation constant was revealed using the example of the formation of the BH3 peptide biological complex of Bmf, Puma, Bad, Hrk, Bax, Bik, Noxa, Bid, Bim and Bak proteins with the Bcl-xL protein and the BH3 peptides protein Bax with the Bcl-2 protein, taking into account the replacement of amino acid residues. Thus, a new method has been developed that allows us to qualitatively determine the l g(Kd) of peptides for full-length proteins and to determine the effect of point mutations in peptides on the stability of the formed complex with whole proteins. A qualitative agreement of the results with Kd on the example of the formation of the biological complex of BH3 peptides of Bmf, Puma, Bad, Hrk, Bax, Bik, Noxa, Bid, Bim and Bak proteins with Bcl-xL (1 200) protein was determined. The influence of point mutations on the stability of the formed biological complexes was also studied on the example of the interaction of the BH3 peptides of the Bax protein in which point replacements of amino acid residues were made with the whole Bcl-2 protein. The formation of the biological complex of BH3-peptide of the protein Bax (49-85) with Bcl-2 was taken as the main interaction The numerical results of the interaction of the protein Bax (49-85) with Bcl-2 were compared with the remaining results of the interaction of BH3 peptides Bax with the Bcl-2 protein taking into account the substitution of amino acid residues. As a result, the Bcl-2 protein regions with the largest number of minimum values of l g were found in the interaction with Bax (49-85). The subsequent analysis of these regions revealed that the other modified BH3 peptides contain much less than the minimum values of l g in the previously designated regions. Thus, it is possible to use the obtained result to determine the binding site of the peptide with the whole protein in order to determine the stability of the formation of the biological complex by any modified BH3 peptide of the Bax protein in which the amino acid residues have been replaced with the Bcl-2 protein. The next stage of the theoretical studies of the interaction of BH3 peptides with proteins of the Bcl-2 family was devoted to find a qualitative correlation between the values of l g and l g (Kd). To perform this comparison, we used the results of the values of l g (Kd) obtained by the interaction of BH3 peptides Puma, Hrk, Bad, Bik, Bax, Noxa with the whole Bcl-xL protein. The result was a qualitative determination of the value of l g (Kd) by analyzing l g. Application of the developed mathematical algorithms will allow us to find the optimal peptides taking into account the affinity for their target proteins and to develop inhibitors or activators of proteins in the future.

Biography

T V Koshlan is currently working as a Professor at Peter the Great St. Petersburg Polytechnic University, Institute of Applied Mathematics and Mechanics, Department of Higher Mathematics. She has completed his PhD in Physics and Mathematics with Mathematical modeling of the optical properties of multilayer biological systems and structures in their heterogeneous conjugation. She has habilitation at the State Polytechnic University (Great St. Petersburg Polytechnic University) of St. Petersburg, Russia (Doctor Science in Physics and Mathematics). Her research interests are diffraction theory, electrodynamics, and physics of lasers, tissue optical methods of mathematical modeling in biological tissue optics and numerical method, biophysics.

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