In silico Mapping of the 14-3-3zeta and TRAF Protein Interactions

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Recent advances show that the 14-3-3zeta protein is a unique regulator of IL-17A signal transduction. IL-17A signal transduction triggers two, 14-3-3zeta-TRAF5 and 14-3-3zeta-TRAF6-dependent intracellular pathways responsible for producing CXCL-1 and IL-6/IL-8, respectively. Improved IL-17A signaling blockers are desirable in treating chronic inflammatory diseases, the world's largest cause of death. Due to its unique role, 14-3-3zeta is an attractive target to regulate IL-6, IL-8, and CXCL-1 levels. This study aims to determine interaction sites between 14-3-3zeta and the TRAF (5 and 6) proteins by utilizing bioinformatic analysis. Using ZDOCK, the binding site between 14-3-3zeta and TRAF (5 and 6) without, then with, restrictions was observed. The mapped interacting residues were mutated, and an effect on the interaction with 14-3-3zeta was observed. To further evaluate the interaction quality, Prodigy was utilized to measure the binding energy for several possible structures and narrow down the selected interaction sites further. The results indicate that site 479-485 on TRAF5 is the putative target of the 14-3-3zeta-TRAF5 complex with a Gibbs free energy of -17.5 kcal/mol and Kd of 1.60x10E-13 M. The results for the TRAF6 experiment indicate that residues 483-488 on TRAF6 interact with 14-3-3zeta with a Gibbs free energy of -19.1 kcal/mol and a Kd of 9.50x10E-15 M. These results provide a rationale to investigate the 14-3-3zeta and TRAF proteins further to develop a future inhibitor therapy. This therapy would have applicability to chronic inflammatory diseases, including autoimmune disease and Coronavirus Disease 2019.

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