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Prediction of protein-protein interaction in the twilight zone of low homology for the modulation of an ion channel: An analogy approach

The tenet of homology modeling relies on the tendency that the divergence of structure directly reflects the variation in amino acid sequence identities. Hence the higher the sequence identity (homology) between a target and a template structure the more reliable the predicted target structure should be. This has been a useful paradigm to generate motifs, folds and domains of the proteins that have not been crystallized. Albeit, the study of dynamic protein-protein interactions (PPIs) that underpins natural phenomena gating ions through cell membrane channels in the present case requires the identification of functional interfaces. Here we demonstrate how a hitherto unknown PPI can be studied even under extremely low homology conditions (far distant phylogenic relationships) by an analogy protein modeling. This approach can overcome the problem of structural uncertainties due to random sequence similarities and can lead to additional insights where three-dimensional data is missing. It proposes what we call; a common epi-homology feature which is neither structure-bound nor related to protein activity. Eventually, it was the distinction between reversibility and irreversibility of PPIs. The finding enabled us to identify two adjacent amino acids at the postulated reversible interface between two subunits (alpha and beta-1) of the skeletal muscle voltage-gated Na+ channel (Nav1.4). A single side-directed mutagenesis study combined with subsequent electrophysiological characterizations provided the proof of concept and validation. The outcome was a double mutant (T109A and N110A, called TANA for short) that caused the highest loss-of-function effect in the literature.
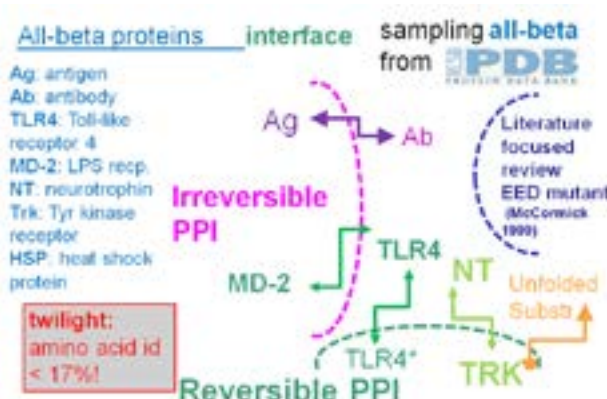
Analogy modeling: Collecting known structures of all-beta proteins showing protein-protein interfaces (PPI) to other proteins regardless of their structural differences and functions (analogy modeling). After superpositioning the location of reversible and irreversible PPI becomes evident. Since a reversible PPI between the alpha and beta subunits (the latter is an all-beta protein) was postulated based on our electrophysiological experiments, all locations of irreversible PPIs were discarded to narrow the search of amino acids on the beta subunit which interact with the alpha subunit of the sodium channel. This procedure lead to the identification of the double TANA mutant in just one circle of site-directed mutagenesis.

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