Mini History

Scientists for many years have been studying transmembrane proteins, but what are these proteins and their function? A transmembrane protein is an integral protein that can pass through the membrane bilayer. These proteins are important molecules because they transport substances through the plasma membrane and are capable of signaling information about the external environment of the membrane to the cell. They act as transporters, receptors, anchors, and enzymes (Shimizu, 2018). In order to gain a better grasp of these proteins, we need to take a deeper look and observe their chemical components. Before technology, scientists would look at chemical structure of the proteins to identify it’s features and functions. With the help of researchers in the mid-1900s, the structures of these proteins were proposed and since then gave the science community a better idea of transmembrane proteins.

In order to understand transmembrane proteins, we have to look deeper into the chemical aspect of its structures. In the fall of 1942 Maurice L. Huggins proposed and compared protein structure models with x-ray and analytical data for silk fibroin, b-keratin, a-keratin, and collagen (Huggins, 1942). He uses basic chemistry to form his hypothesis. He assumes quite a bit throughout this paper, given that not a lot has been discovered yet during this time period. The first assumption is that the attraction between CO and NH groups that produce intermolecular NHO bridges in small molecule crystals also produces similar bridges in proteins (Huggins, 1942). The bridges would then be linked together in rings or long chains capable of resonance and synchronized oscillations of the hydrogens and the mobile electron systems (Huggins, 1942). The x-ray data from silk and b-keratin does not necessarily prove his hypothesis but seems to be in agreement with it with a specific resonance structure with non-coplanar hydrogen bridges. He concludes his research with the proposed structures for silk fibroin, keratin, and collagen cannot be proven, but are in better agreement with the experimental data compared to the other structures proposed. With this information, another scientist can further their knowledge of these proteins and structures to make new discoveries.

Scientists Linus Pauling, Robert B. Corey, and H. R. Branson proposed a-helix and b-sheet in spring 1951. Since 1936 they have been “attacking” the problem of the structures of proteins. One of the ways they have been attacking is the complete and accurate determination of the crystal structure of amino acids, peptides, and other substances that are related to proteins (Pauling, 1951). They constructed two reasonable hydrogen-bonded helical configurations for the chain, which they think are an important part of the structure of fibrous and globular proteins (Pauling, 1951). They look at bond angles, interatomic distances, and configurational parameters in compound structures. They found that two hydrogen-bonded helical structures for a polypeptide chain residues are stereochemically equivalent. The interatomic distances and bond angles have values found in substances related to proteins.

With these studies, later scientists want to pay attention to more detailed aspects of the membrane protein, especially the evolution of membrane protein topology. Two related polytopic inner membrane proteins from *Escherichia coli* evolved opposite orientations. This was apparently achieved by the selective redistribution of positively charged amino acids between polar segments (Sääf, 1999). With this information, a complete inversion of membrane topology is possible with few mutational changes. The function of RnfA and RnfE is not known, but are thought to be involved in mediating electron transport between electron transfer systems. Sääf concludes that RnfA/E pair provides an example of divergent evolution on the level of protein topology.

A few years later in 2003, we look at authors, Guido Tiana, Boris Shakhnovich, Nikolay Dokholyan, and Eugene Shakhnovich, who are attempting to understand the evolutionary origin of protein folds by stimulating their divergent evolution with a three-dimensional lattice model. They focus their research on the proteins progression by sequence duplication and point mutations. The genes are tested on their ability to fold into a stable and unique structure through kinetic folding simulations. The new sequence is accepted and a “new protein structure” is created. Each protein contains a diverse structure through the algorithm. They test the significance of the trend on lattice models and show protein domains found in eukaryotic organisms. This is a significantly higher design ability than prokaryotic counterparts. Their evolutionary algorithm is a 5 step process. They start from the initial structure and design a sequence that can fold stably with the Monte-Carlo design. While the target structure is being fixed, they performed Monte-Carlo in sequence space, at a specific temperature. Randomly evolved proteins are selected and made gene duplication with a point mutation, folding the gene several times starting randomly. If the new sequence folds to its native structure, the gene duplication attempt is accepted and a new protein is born, but if it fails then the gene duplication is rejected. They discovered that a divergent model of protein structure morphogenesis is able to capture the selection of special structures that are observed to be predominant in the protein universe.

 Since we’ve recently in the last decade been able to identify proteins and their functions, it’s hard to observe past research on these transmembrane proteins and their evolution. There is a clear pattern of heavy chemistry that scientists studied in the mid-1900s to get a closer look at these proteins and their structures. Huggins was able to make assumptions throughout his research, given there was not much information, to begin with. Although he was never able to prove his theory’s, he was able to connect different theory’s to his and with this information, later scientists can better understand membrane proteins. Pauling, Corey, and Branson are notably the scientists that are credited for the proposition of the a-helix and B-sheet through the deduction of fundamental building blocks from properties of small molecules (Eisenberg, 2003). Many studies have been made since the discovery of the a-helix and b-sheet structures to better understand transmembrane proteins. The evolution of the science community has transformed greatly in the last few decades. With the help of earlier scientists and recent technology, we are now able to better understand proteins in a much deeper aspect.

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