Inter-residue interactions in membrane proteins

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Abstract- *Knowing the precise 3D-structure of a protein is crucial to understand its functional mechanism at the molecular level and to develop new pharmacological agents to targeting it. Nowadays only a few hundred integral membrane protein structures have been solved at high resolution due to the associated technical difficulties. In the present study we aim to characterize the main interactions in alpha and beta membrane proteins that are responsible of the maintenance of the overall structure. With this purpose, two non-redundant databases of alpha and beta transmembrane segments were constructed and analysed. The interactions that stabilize the structure of alpha and beta membrane proteins were quantified. The results reveal important differences in inter-residues interactions between alpha and beta membrane proteins. This novel structural information may be useful in predicting 3D models of proteins lacking structural information or in refining initial models of alpha and beta membrane proteins.*

I. INTRODUCTION

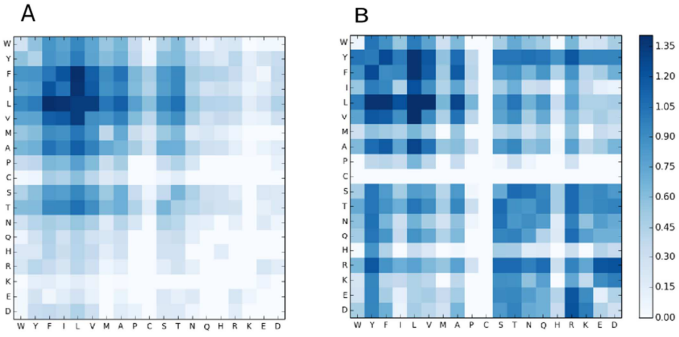
Membrane proteins (MPs) are located in the cell membrane, mediating the interaction between the cell and its surrounding. They include receptors, ion channels, transporters, and enzymes and are involved in multiple cellular processes. Membrane proteins constitute 20%–30% of human genes [1] and represent the targets of over half of known drugs targets [2-5]. With the explosive growing of sequence information that results of massive parallel sequence technology, the gap between sequences and protein 3D structures is still widening. Since experimental structure determination of MPs is such a major endeavor, computational approaches that predict 3D structures of membrane proteins are a valuable tool to complement existing experimental data.
The fact that hydrophilic environment conditions the structure and features of membrane proteins, implies that water-exposed regions of membrane proteins will differ from the membrane-embedded ones. Thus, to study specific structural features of the transmembrane (TM) proteins, it is necessary to distinguish the membrane embedded from the water exposed regions. Several algorithms have been developed to identify the transmembrane spanning regions of membrane proteins [6-7]. Inter-residue interactions have been one of the main focuses to understand the mechanisms of protein folding and stability. Consequently, many methods have been described to explore the amino acid content of a protein and their inter-residue interactions for a variety of goals [8-14]. These studies mainly rely on globular proteins, as these proteins are overrepresented in the Protein Data Bank [15]. The aim of this study is to characterize the inter-residue interactions in membrane proteins that are responsible for maintaining the overall fold. The difference in the nature of interactions for alpha and beta membrane proteins provide clues to the different characteristics of these two types of membrane proteins and its role in stabilization of structures. The quantification of these interactions can be a valuable tool to refine initial molecular models.

II. RESULTS AND DISCUSSION

A. Residue interactions in alpha and beta membrane proteins

The interactions involving hydrophobic amino acids represent the majority of the residue-residue contacts in alpha membrane proteins: L-F, I-F, L-V, L-L, followed by F-I, I-V, F-V, A-L, T-L and F-A (Figure 1-A). Interactions involving polar (S and T) and hydrophobic amino acids also show a high frequency. The frequency of contacts between polar and/or charged amino acids is very low. These results confirm that hydrophobic interactions are the most important contacts that stabilize alpha helical membrane proteins.
In beta membrane proteins, the interactions are spread among a wider type of residue interactions (Figure1-B). The most prevalent interaction is L-L, followed by L-V, F-L and Y-L and then L-A, L-I, and F-Y. Contacts between R and D, E and Y are also found with a high frequency. Polar amino acids interact with hydrophobic ones, like in alpha membrane proteins, but they also interact with charged and polar amino acids with a higher frequency. Contacts between charged residues are also frequently present. On the other hand, R and Y do not show marked preferences for specific amino acids.

Figure 1. Inter-residue interactions matrix. A) alpha membrane proteins and B) beta membrane proteins



III. CONCLUSIONS

- Alpha membrane proteins concentrate residue contacts in one type of interactions, while in beta membrane protein, substantial inter-residue contacts are distributed in a wider type of interactions.

- Hydrophobic interactions appear to be the most prevalent interaction in alpha and beta membrane proteins, although some differences in the prevalence of these interactions are observed. Polar or charged inter-residues interactions have an important role in beta membrane proteins.
- The analysis of inter-residue contacts can be a valuable tool for the prediction of structural models for transmembrane alpha and beta proteins.

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