Mapping the human single-span membrane proteome for self-interacting transmembrane domains

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Single-span membrane proteins comprise more than 10% of the human proteome. Most of those integral membrane proteins form non-covalent functional complexes that are frequently supported by sequence-specific interaction of transmembrane domains (TMDs). It has been suggested that non-covalent membrane protein multimerization may substitute for the frequently observed multi-domain organization of soluble proteins. To date, only a few dimerization motifs such as the GxxxG motif are known. Even those motifs are highly depending on the sequence context.

Here, we investigate biological relevant sequence similarities of human single-span membrane proteins and use them to construct clusters of homologous TMDs. Using the ToxR system it is possible to experimentally determine the self-interaction of one representative TMD for each group. Most tested sequences show medium to high self-interaction. From those findings one can assume specifically interacting TMDs to be highly represented in the human proteome.

We also aligned human single-span membrane proteins with orthologs from other eukaryotes and examined the sidedness of transmembrane helices. We find that almost half of the human transmembrane helices exhibit a non-random conservation moment that correlates well with their ability to self-interact. Additionally, the hydrophobic and volume moments of transmembrane helices increase from lower eukaryotes to higher taxa.

Thus, transmembrane helix-helix interactions may have increasingly contributed to membrane protein assembly during eukaryotic evolution. This might support their functional diversification in complex multicellular organisms. Further experimentally analyses based on this findings will help to identify even rare interaction pattern motifs of transmembrane domains. This allows to study underlying mechanisms and gives insight into how specificity is achieved.

References

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