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Characterization of Transmembrane Proteins with Five Alpha-Helical Regions

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Abstract : Transmembrane proteins are important components in many essential cell processes such as signal transduction, cell-cell signalling, transport of solutes, structural adhesion activities, and protein trafficking. Due to their involvement in diverse critical activities, transmembrane proteins are implicated in different disease pathways and hence are the focus of intense interest in understanding functional activities, their pathogenesis in disease, and their potential as pharmaceutical targets. Further, as the structure and function of proteins are correlated, investigating a group of proteins with the same tertiary structure, i.e., the same number of transmembrane regions, may give understanding about their functional roles and potential as therapeutic targets. In this in silico bioinformatics analysis, we identify and comprehensively characterize the previously unstudied group of proteins with five transmembrane-spanning regions (5TM). We classify nearly 60 5TM proteins in which 31 are members of ten families that contain two or more family members and all members are predicted to contain the 5TM architecture. Furthermore, nine singlet proteins that contain the 5TM architecture without paralogues detected in humans were also identifying, indicating the evolution of single unique proteins with the 5TM structure. Interestingly, more than half of these proteins function in localization activities through movement or tethering of cell components and more than one-third are involved in transport activities, particularly in the mitochondria. Surprisingly, no receptor activity was identified within this family in sharp contrast with other TM families. Three major 5TM families were identified and include the Tweety family, which are pore-forming subunits of the swelling-dependent volume regulated anion channel in astrocytes; the sidoreflexin family that acts as mitochondrial amino acid transporters; and the Yip1 domain family engaged in vesicle budding and intra-Golgi transport. About 30% of the proteins have enhanced expression in the brain, liver, or testis. Importantly, 60% of these proteins are identified as cancer prognostic markers, where they are associated with clinical outcomes of various tumour types, indicating further investigation into the function and expression of these proteins is important. This study provides the first comprehensive analysis of proteins with 5TM regions and provides details of the unique characteristics and application in pharmaceutical development.

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