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Membrane Proteins: New Approaches to Probes, Technologies, and Drug Design

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This two-part special issue focuses on membrane proteins and the new approaches to probes, technologies, and drug design. The selected articles present various novel strategies to study and characterize membrane proteins relevant to both physiological and pathological conditions.

The scientific interest behind membrane proteins has increased over the years due to the knowledge that these proteins represent a key component of cell homeostasis. In fact, virtually all molecules, including water and ions that traffic among cells and, within a cell, among different compartments, need membrane transporters or channels to cross cell membranes to reach the definitive cell location for accomplishing the expected function. In the same scenario, molecules able to regulate cell homeostasis and responsible for transmitting signals, require interaction with specific membrane proteins, the receptors.

The importance of membrane proteins has been made apparent by the occurrence of associated pathologies with a wide range of severity. This makes these molecules very attractive as drug targets. The evidence compels a call to intensify the study on the function, structure, and regulation of membrane proteins with a special focus on the development of novel technologies. The intrinsic difficulty in handling such hydrophobic proteins has hindered progress. Therefore, there are several missing pieces in this cell puzzle.

The first part of the special issue is intended to provide an overview of the status artis with regard to knowledge of the transporters and channels responsible for the traffic of different metabolites and the activity of certain cell surface receptors (G-protein-coupled receptors [GPCRs]).

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The first original research paper by Ciarimboli's group deals with the SLC22 family of organic cation transporters (OCTs) that are responsible for the traffic of organic cations ranging from neurotransmitters to pharmacological compounds.[1] This role makes OCTs highly relevant in cell physiology. Some obscure points are still present with particular reference to the regulation of OCTs. The paper by Ciarimboli describes the interactions of OCTs with tetraspanins CD63 and CD9, which are scaffold proteins responsible for regulating the trafficking and compartmentalization of cell partners. The interaction with OCTs is shown to be potentially relevant for explaining the biological function of these proteins.

The second paper in this special issue is a review by Indiveri et al. on the role of cysteine residues in solute carriers (SLCs).[2] Cysteine is indeed one of the "gainer" amino acids in protein evolution, indicating that its abundance in proteins has increased over time. The presence of a reactive thiol group in its lateral chain makes this amino acid an important targetable residue for drug development. Therefore, studying cysteine reactivity in proteins may represent a straightforward step for improving drug design.

The third paper of the special issue is a review by Leanza and colleagues dealing with the possibility of targeting the mitochondrial potassium channel to block cancer cell growth, proliferation, migration, and metastasis.[3] The paper describes how altered expression of potassium channels is observed in several tumor tissues. This hallmark of human cancers has been exploited for designing new drugs that have been shown to be effective in vitro and in animal models.

The fourth paper is a review from Nesci's group on the mitochondrial ATP synthase.[4] This protein has a long and outstanding scientific history in cell physiology. Its importance has increased over time due to its involvement in the formation of the mitochondrial permeability transition pore (mPTP). The opening and closure of the mPTP plays an important role in regulating cell life and death. This feature makes mPTP an important pharmacological target in different pathological conditions.

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The fifth paper, by Pluckthun et al., is an original research article dealing with novel methodology to study GPCRs in drug discovery.[5] GPCRs are the largest superfamily of integral proteins in the human genome. The presented assay is based on the fluorescence polarization for the neurotensin receptor type 1, which is involved in inflammation and in diseases such as cancer and Parkinson's. This methodological approach could potentially be expanded to large compound libraries and other GPCRs.

The sixth and last paper of the first part of the special issue is by Eberini et al. Their original research work deals with one of the most acknowledged cancer targets among SLC members, SLC6A14.[6] This is a peculiar plasma membrane protein involved in the transport of 18 out of 20 amino acids and of carnitine. The functional and structural studies on this protein are still in their infancy, so homology modeling and molecular dynamics simulation have been used to predict crucial residues for substrate gating and translocation. Therefore, the validation of such predictions will also have a great outcome for the design of new drugs to be used in cancer therapy.

In conclusion, the articles included in the first part of this special issue are a small but comprehensive collection of key aspects in the study of membrane proteins. This may be a pioneering effort for other focused collections in the same field.

With the same scope, the second part of the special issue will deal with the technological novelties applicable to the study of membrane proteins. Innovation in technology is, indeed, primarily responsible for the improvement reached or reachable in the field. However, this aspect also represents the main bottleneck that must be overcome to move relevant steps forward in basic and, hence, applied research.

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