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specific antigens that are expressed by HCC progenitor cells (HcPC). This allows the growth of HcPC into established HCC, a malignant progression that is even further accelerated by total $CD8^+$ T cell ablation. Conversely, genetic and pharmacological interventions that reactivate exhausted $CD8^+$ T cells and unleash their cytotoxic activity result in the regression of established HCC. These findings establish the importance of immunosurveillance in preventing liver cancer and the contribution of a specific immunosuppressive mechanism in alcohol and obesity induced HCC.

SYMPOSIUM XVII
BIOPHYSICAL INSIGHTS INTO PROTEIN STRUCTURE, FUNCTION AND DYNAMICS

THE NICOTINIC ACETYLCHOLINE RECEPTOR AND ITS SURROUNDING LIPIDS: A LONG-STANDING RELATIONSHIP

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The muscle nicotinic acetylcholine receptor (AChR) is one of the key players of the post-synaptic components in neuromuscular junction. It is an integral membrane protein that belongs to the Cys-loop superfamily of ligand-gated ion channels and is composed of four subunits in a pentameric arrangement ($\alpha_2\beta\gamma\delta$ and $\alpha_2\beta\varepsilon\delta$ in embryonic and adult muscle of vertebrates, respectively). Each subunit has a large N-terminal extracellular domain, four transmembrane segments (M1-M4), a small cytoplasmic domain between M3 and M4, and a short C-terminal extracellular domain. Summing up, the AChR has two well defined structural domains: the neurotransmitter-binding site extracellular domain and the transmembrane domain containing the ion pore. Whereas the extracellular domain is the location site of agonists or different activators/inhibitors, the transmembrane region exhibits extensive contact with the surrounding lipids through structural motifs remarkably conserved along phylogenic evolution. It is known that a correct allosteric coupling between both domains is crucial for AChR function, which is strongly dependent on lipid surrounding. We have previously demonstrated that exogenous hydrophobic molecules, such as free fatty acids or steroids, disturb this coupling through the lipid-AChR interfase. It is also known that the AChR is present in high-density clusters at the top of folds in the muscle cell membrane, and that these clusters localize in heterogeneous membrane domains highly enriched in cholesterol (Chol) and sphingolipids. We studied the influence of different lipid host compositions on the distribution of purified AChR reconstituted in membrane containing Lo domains by fluorescence resonance energy transfer efficiency between the AChR intrinsic fluorescence and Laurdan or dehydroergosterol fluorescence, and by analyzing the distribution of AChR in detergent-resistant and detergent-soluble fractions (1% Triton X-100, 4°C). When the AChR was reconstituted in a brain sphingomyelin (bSM), Chol and POPC (1:1:1) model system it lacked preference for Lo domains. However, the change of bSM by 16:0-SM or 18:0-SM resulted in the preferential partitioning of AChR in Lo domains, which was not the case with 24:1 SM. Although all these SM formed Lo domains, differences in size, amount and/or lipid order of each Lo domain were observed, showing a direct correlation with the tendency of the AChR to localize in such domains. We further studied another membrane condition resulting from inducing transbilayer asymmetry. Enrichment in bSM in the external hemilayer resulted in an increase of the amount of external domains with a higher lipid order and a marked increase of AChR in these Lo domains. Other asymmetric conditions were also studied. Thus, a change in the properties/size/location of Lo domains impacts on the AChR preference for this fraction, clearly indicating that membrane lipid surrounding influences both the coupling between agonist-binding and channel-gating domains and the spatial localization of the AChR in the membrane.

A METASTABLE H-BOND ZIPPER TRANSMIT INFORMATION ACROSS THE CELL MEMBRANE

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Transmission of information across cell membranes is an essential activity for every cell. Bacterial thermosensor DesK is a histidine-kinase endowed with a five-span transmembrane domain that detects changes in environmental temperature and controls the phosphorylation state of its cytosolic catalytic domain. The challenge for most systems is to understand the mechanistic basis of signal transmission across the cell membrane, in order to either inhibit or potentiate signaling. To address the challenge, we constructed a sensor with a single chimerical transmembrane segment that retained full sensing capability. Genetic and biophysical dissection of this minimized DesK version enabled identification of three structural determinants of thermo-detection (DOTs). Here we combine and retune these DOTs to understand their interplay, dominance and over-writing effects according