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Editorial

Cell Surface Receptors in the 21st Century

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It is a pleasure to be given the opportunity to edit this special issue on Cell Surface Receptors.

Receptors are molecules that sit on the plasma membrane of cells, receive signals from the extracellular environment usually in the form of hormones (but could be also light or mechanical pressure) and transmit these signals to the cell interior. Cells use this information to make "decisions" to move, grow or die. Not surprisingly, receptors play important roles in normal physiology, during development and growth, and in maintaining homeostasis. Our daily mental activities are also under the control of receptors and these dictate experiences such as taste, mood, and appetite. Conversely, receptor malfunctions are often associated with pathological conditions for example in cancer and diabetes where messages are inappropriately transmitted. It is not surprising that there is an enormous academic and industrial interest in cell-surface receptors. Receptors are associated with about 30% of the drugs that are on the market today.

The first challenge is to understand at atomic level, the mechanism by which receptors are activated and/or inhibited. This means that we need to determine the three-dimensional structure of receptors. Like all membrane proteins, receptors are water-insoluble. This presents problems in terms of purification and crystallization for x-ray structural studies. The rates of translational and rotational motion are also inhibited in the viscous membranes making traditional NMR difficult. Despite these challenges only a few complete structures have been solved. Many more structures of water-soluble fragments of receptors are available and one can use these structures together with lower resolution techniques that are applicable to model membranes and living cells. Techniques such as solid-state NMR, EPR (DEER), and fluorescence can be used to obtain information about orientation, distances and dynamics of labelled sites on receptors. This information in turn can be employed to distinguish between different models of receptor activation. Where biophysics can help here is in the development of methods that can bridge the gap between atomic level structures and actual cell surface structures. The development of long time-scale molecular dynamics simulations and super-resolution microscopy where the resolution of the microscope is increased down to 10–20nm are important steps in the right direction.

The second challenge is to understand how the organisation of receptors within the 3D structure of the cell influences functioning. It is well understood that the transverse organisation (cell surface, coated-pits, endosomes, vesicles, ER, Golgi) is important in terms of receptor activation, receptor deactivation and receptor reactivation but it is less well understood how the lateral organisation of receptors influences activation and transactivation. Do receptors act alone as monomers, in pairs as in receptor tyrosine kinases or in higher-order oligomers as in the bacterial chemotaxis receptors? How does receptor organisation between two different receptors impact on receptor cross-talk? What is the role of lipids, cholesterol, actin cytoskeleton and membrane "rafts" indictating receptor quaternary structure and function?

The third challenge is to understand how structural models derived from cell biophysics approaches can be used to predict cell decision-making processes. An experimental approach might involve linking receptor structure, receptor activation and cell fate. This is where functional microscopy approaches can be of value. In silico theoretical biophysics can also play a large role since the underlying signal transduction network as well as the receptor structures can be modelled together. This is particularly true in the face of combinatorial complexity of the structural and chemical (post-translational modifications) receptor states. In this circumstance literally trillions of states can possibly exist and any intuitive or simple model fails. However predictions of the measurement outcome of a single property, such as phosphorylation, can be modelled and linked to experiment.

The fourth and final challenge is to use the combination of theoretical biophysics and experimental biophysics to design drug targets for intervention. The parameters here are what, where, when and how many. Can we design a wonder drug that binds to an ATP pocket on a receptor tyrosine kinase that shuts off a receptor-dependent cancer? Or do we really need to add four drugs to shut off all proliferation and metastasis of an aggressive cancer? Here the combination of biophysics, chemical biology and nanotechnology with oncology, pharmacology and neurobiology is important. Since biophysics is already a mature multidisciplinary field we should take centre stage in addressing these challenges.

I hope you enjoy this issue on Cell Surface Receptors.