Effects of clustering and phosphorylation on nanoscale receptor signalling

Supervisory team:
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Project description:
Heart muscle cells contain a key receptor protein, the ryanodine receptor (RyR), which is an intracellular calcium channel. Muscle cell contraction is enabled by transient increases in cellular calcium levels, termed calcium transients, which result from calcium released through RyRs.

Recently it has been recognized that cell function can be greatly affected by modulation of receptor clustering. Receptor clustering refers to the close grouping of RyRs within intracellular membranes so that adjacent receptors are only few tens of nanometers apart. These groups come in many different sizes and contain between just a few to >100 receptors.

This project aims to improve our understanding how receptor clustering makes activation of these receptors more effective, and what happens if the clusters contain too few or too many receptors. To investigate this behaviour we will employ two microscopy techniques. The first technique is designed to accurately measure the clustering of proteins in intact cells, as well as their phosphorylation state. This requires imaging receptor distributions with molecular resolution which we have achieved with optical super-resolution imaging so that we can “see” individual biomolecules and count the number of RyRs in clusters (see also the image of RyR clusters in Fig. 1). The second technique uses calcium sensitive dyes imaged with a confocal microscope to directly see the calcium released through RyR clusters. By combining the two approaches we will determine how cluster size affects the amount and frequency of calcium being released through RyRs.

In collaboration with colleagues in Cardiff we have identified a protein which modulates the clustering of RyRs. This protein, called myospryn, increases RyR clustering (i.e. causes more receptors to be within a closely packed group) when overexpressed. We will use this to modulate RyR clustering and observe how cell function, measured via monitoring the calcium released through RyRs, is altered. To obtain insight how to predict cell function we will construct a mathematical model to allow us to predict the amount and frequency of calcium release resulting from any pattern of receptor clustering. The model will be based on a previously investigated simpler model that will be extended by using the new data generated here. Our insights could lead to novel treatment strategies aiming to rectify problems resulting from faulty receptor clustering.

The student will receive training in advanced fluorescence imaging, molecular biology, quantitative image analysis and mathematical modelling in the new interdisciplinary Living Systems Institute in Exeter.