Dissecting how cells communicate to prevent cancer relapse

Protein kinases are a class of enzymes that are responsible for the transfer of phosphates onto other proteins. These phosphate groups, although small, can change the behaviour of the protein itself, or the behaviour of those it interacts with. This process is commonly used for cells to communicate to one another and to respond to changes in their environment. This is very important for a number of different biological processes, but has also been shown to be very important in cancer. Protein kinases form complex networks that allow them to spread messages between each other. As a result, a single kinase can have a big impact on the behaviour of many other kinases and therefore help cells to survive and overcome stresses in their environment.

As a result of their importance in cancer, kinase-targeted drugs have been at the forefront of advances in personalised/targeted treatments for several different kinds of cancer for several years. Unfortunately, however, those cancers that initially respond to kinase-targeted therapies eventually acquire resistance, and this can ultimately lead to relapse. Consequently, trying to understand how cancers evolve in response to targeted therapies is an important area of research; the ultimate aim of which being to understand how to prevent the occurrence of resistance in the first place and make these treatments more successful.

Using a technique called mass spectrometry, the amount of phosphorylation on thousands of different proteins can be measured simultaneously. In this paper we used this information to understand how different kinases talked to one another in their networks, and to understand how this changed when cells were treated with targeted drugs. We found that the complexity of the network was greater than has been previously appreciated – this significantly adding to our knowledge of the structure of these networks and how they behave. Measuring the activity of the network in cells that were initially identical, but had been treated to acquire resistance to two kinase-targeted therapies, revealed that these networks underwent substantial change. Most importantly, we noticed that these changes were different between initially identical cells treated with the same drug. This suggested that, although the cells were identical at the beginning of the experiment, they developed different responses to the drugs. This has potential implications for other cancers, as seemingly identical tumours may respond differently to the same drug in an unpredictable manner. This knowledge brings us closer to understanding how resistance develops and how best to combat it in the future.

Publication

Empirical inference of circuitry and plasticity in a kinase signaling network..
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