

Jekyll and Hyde protein signalling

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Whether a cell lives or dies is determined by complex protein networks within the body. Researchers in Systems Biology Ireland and UCD Conway Institute have uncovered how these opposing biological functions are regulated by the same elements in protein networks.

Using a combination of molecular biology and mathematical modelling, the team led by Professor Walter Kolch looked at a particular protein network that plays an important role in cancer. The Hippo/MAPK signalling network regulates cell proliferation and apoptosis.

The findings of their research, published in the current issue of *Nature Cell Biology*, describe the molecular mechanisms and kinetics that determine the Hippo/MAPK network outcomes.

Describing the findings, lead author and postdoctoral researcher, Dr David Romano said, "We wanted to understand how specific decisions are made by a given protein network where the same elements regulate mutually exclusive cell fates.

We show that competing protein interactions and changes in protein affinity caused by phosphorylation coordinate the opposite signals regulated by the Hippo/MAPK network. These [protein interaction](#) switches seem to be common in many [protein networks](#) and the result of this work can be generalised to other systems."

Many diseases such as cancer, diabetes and Alzheimer's occur when genetic mutations disrupt the normal organisation of protein networks.

For many years, the therapies developed to treat these diseases focused on targeting single proteins within these networks with limited success. Protein networks can become re-wired and the cell develops resistance to treatments over time.

Professor Walter Kolch explains, "In order to get a better understanding of cancer development and design more effective anti-cancer treatments, we need to understand how protein networks function and determine different outcomes. The results of the current work are a step in that direction and could eventually help to develop better cancer treatments, which is our ultimate goal at Systems Biology Ireland."

The study used molecular biology to examine the changes of protein interactions in cancer cell lines. The team carried out experiments in the UCD Conway flow cytometry facility to understand the [biological functions](#) regulated by the Hippo/MAPK network. They used ordinary differential equations to develop the mathematical model that integrates the experimental data and existing data from the literature. The mathematical model predictions allowed them to generate new hypotheses that could not have been formulated by using an experimental approach alone. The hypotheses were validated experimentally allowing identification of the molecular mechanisms that govern the Hippo/MAPK network.

More information: Romano D, Nguyen LK, Matallanas D, Halasz M, Doherty C, Kholodenko BN, Kolch W. "Protein interaction switches coordinate Raf-1 and MST2/Hippo signalling" (2014). *Nature Cell Biology*. July 16, 7. www.nature.com/ncb/journal/vao...nt/full/ncb2986.html

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