# Negative feedback makes cells 'sensitive'

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New research has shown that negative feedback loops in cell signalling systems can be essential for a cell's ability to perceive the strength of a growth stimulus. Cells lacking the feedback loop became insensitive to the level of the stimulus in a manner similar to a cancerous cell displaying unrestrained growth.

Living cells need to sense changes in their environment reliably in order to make appropriate decisions. The biomolecular machinery they use to perform these tasks is surprisingly noisy. Combining automated cell imaging and mathematical analysis, the team from the University of Bristol explored what happens when the signalling system in the cell has a background level of activation even when no stimulus is present, similar to a light bulb that glows even when its switch is off.

The collaborative study, carried out by the groups of Dr Clive Bowsher in the School of Mathematics and Professor Craig McArdle in the School of Clinical Sciences, is published online this week in *PNAS*.

Using information theory and statistics to analyse the data from images of hundreds of thousands of individual cells, the team showed that mutant cells lacking the negative feedback loop could not detect the level of growth factor.

"Breaking the feedback loop resulted in a dramatic and surprising reduction in the information the cell has about its environment," said Dr Margaritis Voliotis in the School of Mathematics and MRC Fellow on the team.

Dr Bowsher, who led the study, explained: "We realised that basal activity can be high enough in kinase signalling to create a dichotomy: the networks with negative feedback continue to function as effective sensors while the mutant networks do not."

Basal activity of signalling pathways is often raised in disease, and the interplay between basal activity and negative feedback is known to be important in cancers like melanoma. The research is expected to improve understanding at the molecular level of how decisions are made by healthy cells and of how signalling goes wrong in diseased cells.

**More information:** Information transfer by leaky, heterogeneous, protein kinase signaling systems, by Margaritis Voliotis, Rebecca M. Perrett, Chris McWilliams, Craig A. McArdle, and Clive G. Bowsher, *PNAS*, published online 6 January 2014.

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