'Switch off, light on': Molecular biologist discovers new control mechanism in cell signalling

February 17 2009

Manuela Baccarini of the Centre for Molecular Biology of the University of Vienna, Austria, investigates a group of proteins which are important for cell division and therefore also for uncontrolled cell growth as occurring during cancerogenesis. Some experiments now lead her together with her team to an unexpected trace: she discovered an unknown regulation mechanism of the MEK enzymes, the key elements of the MAP signal transduction pathway. The results of this FWF project are now published in the journal *Nature Structural & Molecular Biology*.

The MAP Kinase signal transduction pathway plays an important role in embryonic development as well as in differentiation, growth and programmed cell death of human cells. “The enzymes Raf/MEK/ERK are important for cell division and therefore also play a role in uncontrolled cell growth leading to cancer. With a targeted destruction of the genes of these enzymes we can investigate the intended defects and their molecular cause in certain tissues“, says Manuela Baccarini of the Max F. Perutz Laboratories of the University of Vienna.

It is particular for the MAP Kinase pathway that several enzymes with an apparently same function can be found at the key sites of its regulation. For their experiments Baccarini’s group chose the enzymes MEK1 and MEK2, sister enzymes acting at the same site of the signal pathway. “We wanted to know what’s happening at the molecular level in

the cell, if we switch MEK1 off, an enzyme absolutely essential for the embryonic development", explains Baccarini. The results were more than surprising. "We would have expected that so to speak the light is turned off, if the light switch is turned off. But exactly the contrary occurred: the „light switch", the MEK1 gene was switched off, but the sister enzyme MEK2 was exceedingly active and not turned off as well, as we would have expected. Cell division and growth were running at full steam as a consequence of the undisturbed or even increased signal transduction."

Baccarini's experiments show, that the enzymes MEK1 and MEK2 fulfil a similar but not the exact same function in the signal transduction pathway as assumed so far. A further result: the two sister enzymes act as a coherent complex (heterodimer). If one part of the complex (MEK1) is destroyed, the other part (MEK2) can't be switched off correctly anymore. The regulation at this site therefore is based on a so called negative feedback loop.

Development of new therapeutic approaches

Disorders of the MAP Kinase pathway are already known in humans, they manifest amongst others as Noonan Syndrome or Leopard Syndrome. Affected patients show malformation in their appearance, heart diseases and an increased risk of cancer. "A better comprehension of these regulation mechanisms is essential for the development of new therapeutic approaches", says the researcher.

In her further research projects Baccarini will carry on to investigate the influence on cancerogenesis of the MAP Kinase pathway. And another essential task for her: With the management of the "Doctoral Programme Plus" funded by the FWF Manuela Baccarini and the participating research groups at the Max Perutz Labs can educate young academics on highest international level focusing on signal transduction.

More information: Catalanotti F, Reyes G, Jesenberger V, Galabova-Kovacs G, de Matos Simoes R, Carugo O, and Baccarini M: "A MEK1-MEK2 heterodimer determines the strength and duration of the ERK signal" in: *Nature Structural & Molecular Biology*, www.nature.com/nsmb/journal/va … nt/pdf/nsmb.1564.pdf

Source: University of Vienna