New discovery about growth factor can be breakthrough for cancer research

September 2 2008

A research team at the Ludwig Institute and Uppsala University has discovered an entirely new signal path for a growth factor that is of crucial importance for the survival and growth of cancer cells. This discovery, published in today's issue of *Nature Cell Biology,* opens up an entirely new landscape for research on breast and prostate cancer, among other types.

Our cells' ability to understand signals from various growth factors is critical for normal fetal development. The aggressiveness and capacity for survival in cancer cells are also governed by a number of growth factors, with transforming growth factor b (TGF-b) playing a prominent role. In the present study, researchers at the Ludwig Institute for Cancer Research and the Department of Genetics and Pathology, Uppsala University, have identified an entirely new signal path that is regulated by TGF-b.

"This discovery is of tremendous importance for our ability to identify what signal paths TGF-b uses to inhibit the growth of cells, or to stimulate the ability of cancer cells to survive and metastasize," says Marene Landström, who directed the study.

TGF-b conveys its signal to the inside of the cell via receptors bound to the cell membrane in a way that is similar in the great majority of animals. Just over ten years ago, scientists discovered so-called Smad proteins, which serve as unique messengers for the active TGF-b signal. These proteins are activated when phosphate groups bind to them in a

manner that is dependent on enzyme activity (of serine-threonine kinases) in the TGF-b receptors.

The new signal path that the research team has now identified is regulated quite independently of this serine-threonine kinase activity, which makes the discovery published in the article extremely interesting. The study shows that the receptors are used instead to activate another enzyme, TRAF6, which binds to the complex of receptors. TRAF6 is a so-called ubiquitin-ligase, which, when activated, places short little protein chains on itself and other proteins. TRAF6 therefore functions as a switch that can determine what signals should be turned on in the cell. TRAF6 is used by TGF- to be specifically able to activate a kinase called TAK1, which subsequently activates other so-called stress-activated kinases, leading to cell death.

“The discovery that TGF- makes use of TRAF6 to activate signal paths in cells opens up an entirely new landscape for future research. The makes it possible to develop new treatment strategies for advanced cancers that are dependent on TGF- , for example in advanced cases of breast and prostate cancer.”

Source: Uppsala University