Scientists discover new link in pathway to cancer: hope for drug design

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(PhysOrg.com) -- University of Manchester scientists have identified an exciting connection between a cell's extracellular environment and the activity of a signalling pathway molecule that controls the development of organs and tissues, as well as cancer and kidney disease.

Dr Hilary Ashe and her team at the Faculty of Life Sciences hope their work will help develop drugs targeting the pathway, which is known to be involved in 90% of pancreatic cancers and 60% of colorectal cancers, or to activate the pathway and thus reverse kidney disease.

Their study, published in *Nature* (August 2008), showed that human type IV collagen in the extracellular matrix around the cells binds a human BMP signalling molecule.

During development cells communicate with each other by releasing signalling molecules (chemical signals). Other cells receive and interpret these signals in order to determine which type of tissue or organ they will form.

The signalling molecules which exist in the fruitfly Drosophila melanogaster are the same as those which control development in humans. BMP signalling molecules are one of the major signals used during human and fly development. In humans, BMP signalling is necessary for the development of many major tissues and organs, such as the nervous system, kidney, lungs and skin.

In addition cells are surrounded by a network of proteins called an extracellular matrix with one form consisting of type IV collagen proteins. The relationship between type IV collagen and the BMP signalling molecule formed the basis of the BBSRC-funded study.

Dr Ashe explained: “Our study has shown that BMP signalling molecules released by cells bind to the type IV collagen extracellular matrix. As a result, type IV collagens regulate the movement of BMP molecules and their ability to signal after they are released by cells. Therefore type IV collagens control the level of BMP signalling molecules that cells become exposed to, which in turn determines cell identity.

“We have also shown that human type IV collagen binds a human BMP signalling molecule, suggesting that the regulation also exists in vertebrates.”

She added: “As alterations in the activity of BMP and type IV collagen molecules can lead to cancer and kidney diseases respectively, our data will ultimately have important implications for human disease.

“The BMP signalling pathway initially acts as a tumour suppressor but when a tumour becomes malignant, it uses the pathway to become aggressive and spread to other parts of the body. The numbers are incredible – we know that 90% of pancreatic cancers and 60% of colorectal cancers will have an alteration in this signalling pathway.

“In addition part of the collagen we have identified as important has tumour suppressor activity so we believe that when the BMP pathway is being exploited by aggressive tumours the collagens are counteracting this. This is another facet to be investigated.

“Finally type IV collagen is also important in kidney development and disease. This signalling pathway promotes kidney development and

kidney disease is caused by disruptions to these collagens. In fact a previous study has shown that if you make this pathway more active you can reverse kidney disease, so further work could help design therapies in this area as well.

“This study has given us a new area to manipulate, making tumours more or less aggressive, by controlling how active this pathway is. In the future we could see compounds that are designed to make the regulation stronger, to work against a tumour or reverse kidney disease.”

Provided by University of Manchester

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