Understanding cell organization to tackle cancer

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Scientists at The University of Manchester have identified how cells know which way up they need to be. The discovery could help in the fight against cancer because in the early stages of the disease the cells become disorganised.

Professor Charles Streuli and Dr Nasreen Akhtar of the Wellcome Trust Centre for Cell-Matrix Research have conducted new research that leads to a better understanding of cell polarity. Properly organised tissues are vital to maintaining functional organs and a healthy body. Part of being organised includes cells being in the correct position within the tissue and the right way up, because the top and bottom of cells have different functions.

The extracellular matrix (ECM) is a layer of protein rich material that surrounds tissues and helps to design and shape all of our organs. Previous studies have demonstrated that the ECM sticks to the cells and guides them into the right position. What hadn't been identified is how the ECM communicates that message.

To understand this better Professor Streuli and Dr Akhtar looked at epithelial cells, which make up the majority of tissues within the body. They studied epithelial cells of the breast, which make milk. These cells also form the linings of mammary ducts to carry milk towards the nipple. It's vital that these cells are organised correctly in order to make milk accessible for the baby. One of the first signs of cancer is that the epithelial cells become disorganised.

Breast epithelial cells connect to the ECM through receptors called integrins. In experiments using mice Professor Streuli and Dr Akhtar removed one of the genes responsible for integrins. They found that without that gene, the cells were both the wrong way round and in the wrong place so the breast tissue became disorganised. They then tried removing integrins in cultured cells from the breast, which produced the same effect of disorder.

Further study revealed that within the cell the integrin receptors connect to the protein ILK. This protein then links to microtubules, a network that forms the transport machinery of the cell. Integrins and microtubules ensure that inside the cell the correct proteins are transported to the top and the bottom of the cell.

The findings have been published in the journal *Nature Cell Biology*. Commenting on the research Professor Streuli says: "What we identified is a vital interplay between the transport machinery and the integrin receptors which makes sure that proteins are transported to the correct area of the cell. Without this interplay the proteins end up in the wrong place, and this can lead to cells becoming disorganised."

He continues: "What's really interesting is that when we compared breast tissue from our experiments with tissues of patients with early forms of breast cancer, they looked very similar. The cells were upside down and disorganised so they couldn't carry out their functions. We hope that our work to better understand cell polarity could ultimately lead to better diagnosis for cancer patients."

Whilst Professor Streuli and Dr Akhtar only looked at epithelial cells within the breast, they are confident their findings will translate to other organs. The accuracy of their experiments was greatly increased through the use of special 3D cultures to grow the cells, where they form tiny organs that look remarkably similar to real breast tissue.

Dr Akhtar explains: "Growing the breast cells so that they can form 3D structures rather than on hard petri dishes means they develop in a way that is much more akin to how they grow in the body. We were one of the first groups in the UK to be using this technology and we've been really pleased with the results."

Dr Akhtar has been working on this research for five years. She says: "I've been touched by cancer in my own family so I'm really passionate about understanding this devastating disease better. Over 90% of cancers come from epithelial cells, which is why we chose to study them. It's fundamental to understand how healthy cells work properly in order to fully appreciate why they go wrong when cancer develops, and how best to combat the disease."

The next stage of the research will be to investigate the link between altered levels of integrin and cancer, to determine whether this causes the disorganised nature of cells seen in the early stages of the disease.

More information: The paper is titled: "An integrin-ILK-microtuble network orients cell polarity and lumen formation in glandular epithelium".

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