Cells united against cancer

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Sheets of highly organized epithelial cells line all the cavities and free surfaces of the body, forming barriers that control the movement of liquids and cells in the body organs. The organized structure of normal breast epithelial cells may also serve as a barrier against cancer, according to a study by University of Helsinki scientists. The work appears this week in the online edition of the *Proceedings of the National Academy of Sciences*.

Finnish researchers found that the tightly organized architecture of mammary epithelial cells is a powerful restraint against the cancer gene provoked inappropriate proliferation. Their study also links function of a tumor suppressor gene to the development of cancer gene resistant epithelial organization.

"Rogue cancer genes can force epithelial cells to proliferate and proliferation of malignant cells will certainly disrupt the organized epithelial structure. However, there has always been this chicken or the egg problem: Does cancer gene initiate cell proliferation, which causes disruption of the epithelial structure or does loss of tissue structure come first, creating suitable environment for cancer genes to enforce the cell cycle progression?" explains the research team leader Juha Klefstrom, Ph.D. The present study supports the idea that loss of tissue structure comes first.

Experiments with fly models have shown that loss of epithelial organization can enhance the tumorigenic potential of cancer genes (oncogenes) and these findings prompted Juha Klefstrom's team to

explore whether the formation of epithelial organization works other way around and suppresses oncogene function. "We were amazed to find out that the formation of organized mammary epithelial architecture in three-dimensional organotypic cell culture correlated with complete loss of oncogenic activities of c-Myc cancer gene" says Klefstrom.

Johanna Partanen, a graduate student in Klefstrom's laboratory and lead author in the article, continues "We also asked how to dismantle the proliferation resistance of the epithelial organization. To find clues to genes involved in the development of organized epithelial structure, we turned back to fly". Epithelial cells of both flies and humans live their lives in the companionship of others, held together by tight belt of adhesion proteins and interactions with supporting extracellular matrix. Developmental geneticists working with fly models have identified an important group of genes, PAR genes, which regulate the development of highly ordered epithelial cell organization.

"Most interesting candidate for us was LKB1, the human homologue of Par4 protein, because this gene has strong connection to human epithelial disorders" says Partanen. Previous research done by Akseli Hemminki, Lauri Aaltonen and Tomi Mäkelä at the University of Helsinki has linked this gene to Peutz-Jeghers cancer predisposition syndrome and it has also been suggested that LKB1 has tumor suppressor functions in several epithelial cancers. Klefstrom's team found that epithelial cells missing the LKB1 protein are able to form only cancer-like disorganized epithelial structures. This disorganized environment enables c-Myc oncogene to drive inappropriate cell proliferation.

The study demonstrates that organized epithelial structure can suppress malignant actions of cancer genes and identifies LKB1 tumor suppressor gene as an architect of this proliferation resistant organizational plan. The ordered structure of epithelial cells is frequently lost in epithelial tumors, like breast carcinoma, and the study suggests that loss of

structure may play more active role in progression of tumors than previously anticipated.

Source: University of Helsinki