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Lab-made tissue picks up the slack of Petri dishes in cancer research

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New research demonstrates that previous models used to examine cancer may not be complex enough to accurately mimic the true cancer environment. Using oral cancer cells in a three-dimensional model of lab-made tissue that mimics the lining of the oral cavity, the researchers found that the tissue surrounding cancer cells can epigenetically mediate, or temporarily trigger, the expression or suppression of a cell adhesion protein associated with the progression of cancer. These new findings support the notion that drugs that are currently being tested to treat many cancers need to be screened using more complex tissue-like systems, rather than by using conventional petri dish cultures that do not fully manifest features of many cancers.

"Research on cancer progression has been drawn largely using models that grow cancer cells in plastic dishes. Our research reveals a major shortcoming in the experimental systems used to study cancer development. When using simplified culture systems in which cells are grown on plastic, cancer cells grow as a two dimensional monolayer and lack the three-dimensional tissue structure seen in human cancer. As a result, complex interactions that occur between the cancer cells and the surrounding tissue layers are not accounted for," said first author Teresa DesRochers, PhD, a graduate of the Sackler School of Graduate Biomedical Sciences at Tufts, currently in the department of biomedical engineering at Tufts University School of Engineering.

The researchers report that the three-dimensional network of cell interactions activates epigenetic mechanisms that control whether genes

critical for cancer development will be turned on or off. By imitating the structure of the tumor microenvironment seen in different stages of cancer, the research team was able to observe that cell-to-cell interactions that are inherent in tissue structure are sufficient to turn on the cell adhesion protein, E-cadherin, that can delay cancer development.

Since both invasion and metastasis occur when cells break away from the primary cancer site, an event correlated with loss of E-cadherin, treating cancers to induce re-expression of this protein through epigenetic control may be an important way to control cancer progression.

"Our findings show the reversible nature of E-cadherin when cancer cells are placed in a three-dimensional network of cells that mimics the way cancer develops in our tissues. This confirms that cancer biology needs to move into the "third dimension" where cancer cells can be studied in a network of other cells that can control their behavior. We know now that the plastic dish alone is not good enough," said senior author Jonathan Garlick, DDS, PhD, a professor in the oral and maxillofacial pathology department at Tufts University School of Dental Medicine.

Jonathan Garlick is also a member of the Cell, Molecular & Developmental Biology program faculty at the Sackler School at Tufts and the director of the Center for Integrated Tissue Engineering (CITE) at Tufts University School of Dental Medicine.

This study, published in the January issue of *Epigenetics*, was performed in collaboration with Laurie Jackson-Grusby, PhD, associate in pathology at Children's Hospital, Boston, and assistant professor at Harvard Medical School. Additional authors of the study are Yulia Shamis, MSc, a PhD student at the Sackler School of Graduate Biomedical Sciences; Addy Alt-Holland, MSc, PhD, an assistant professor at Tufts University School of Dental Medicine; Yasusei Kudo,

DDS, PhD, and Takashi Takata, DDS, PhD, both of the department of oral and maxillofacial pathobiology, Graduate School of Biomedical Sciences, Hiroshima University, Japan; and Guangwen Wang, PhD, previously a fellow at Children's Hospital Boston, now a senior scientist at Stemgent.

More information: DesRochers TM, Shamis Y, Alt-Holland A, Kudo Y, Takata T, Wang G, Jackson-Grusby L, Garlick JA. Epigenetics. 2012 (January); 7 (1): 34-46 "The 3D tissue microenvironment modulates DNA methylation and E-cadherin expression in squamous cell carcinoma."

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