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How a tumor suppressor helps control changes in cell shape and motility that are central to metastasis

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Ludwig Oxford researchers have discovered a key mechanism that governs how cells of the epithelia, the soft lining of inner body cavities, shift between a rigid, highly structured and immobile state and a flexible and motile form. Published in the current issue of *Nature Cell Biology*, their study shows that a tumor suppressor protein named ASPP2 functions as a molecular switch that controls this process and its reverse, both of which play a critical role in a number of biological phenomena, including wound healing, embryonic development and, not least, the metastasis of cancers.

"We were trying to identify molecular switches that control the plasticity of epithelial cells," says Ludwig Oxford director Xin Lu, who led the study with Yajun Guo of The Second Military Medical University in Shanghai, China. "Such plasticity is a hallmark of cancer. In order to metastasize, a settled cancer cell must loosen its structure, wiggle free from its confines, travel to another part of the body and, once there, settle down to form a colony. Both processes, known as epithelial to mesenchymal transition and mesenchymal to epithelial transition (or, EMT and MET) are necessary for that to happen."

Lu and her team find that ASPP2 contributes to MET in the development and maintenance of kidney tubules, which filter waste out of the blood stream. Its absence, however, does not completely disrupt the process. Loss of ASPP2 expression dramatically promotes EMT,

especially in cells that express a common cancer gene known as oncogenic RAS, which also drives metastasis.

Further, the researchers show in a mouse model that when breast cancer cells express low levels of ASPP2, they metastasize furiously to the brain; if those cells are forced to express the full ASPP2 protein, their ability to metastasize declines significantly. When they express only the portion of ASPP2 that drives MET, however, they actually metastasize a bit better than do the control cells. "This underscores the importance of MET in the final stages of a cancer cell's metastasis, when it establishes a new malignant colony," says Ludwig Oxford's Yihua Wang, co-lead author of the study.

An analysis of liver and breast tumors taken from patients reveals that the findings have clinical significance: poor ASPP2 expression in these cancers correlates with significantly lower patient survival.

Lu and her colleagues discovered that ASPP2 controls MET and EMT through its association with two proteins involved in establishing the junction between epithelial cells: E-cadherin and β-catenin.

It does so by anchoring β-catenin to the junction, both directly and by promoting its association with E-cadherin. This prevents β-catenin from zipping down to the nucleus, where it can fuel the expression of genes that drive EMT—and metastasis. Oncogenic RAS has the opposite effect, which is why cells lacking ASPP2 and expressing oncogenic RAS undergo EMT very efficiently.

"While we have learned a great deal about the drivers of EMT in recent years, much less is known about the inducer of the reverse process, MET, which is equally important to both healthy development and cancer metastasis," says Lu. "This study has identified a new inducer and a gatekeeper of MET."

More information: ASPP2 controls epithelial plasticity and inhibits metastasis through beta-catenin-dependent regulation of ZEB1 , *Nature Cell Biology*, DOI: 10.1038/ncb3050