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Landmark study describes prostate cancer metastasis switch

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Prostate cancer doesn't kill in the prostate – it's only once the disease travels to bone, lung, liver, etc. that it turns fatal. Previous studies have shown that loss of the protein E-Cadherin is essential for this metastasis. A University of Colorado Cancer Center study published this week in the *Journal of Biological Chemistry* describes for the first time a switch that regulates the production of E-Cadherin: the transcription factor SPDEF turns on and off production, leading to metastasis or stopping it cold in models of prostate cancer.

"When E-Cadherin is lost, cells become 'rouge' – they can detach from their surrounding tissues, move effortlessly through the circulatory system, grow and attach at new sites. In prostate tumors that had lost E-Cadherin, we put in SPDEF and the tumors once again expressed E-Cadherin. They were once again anchored in place and unable to metastasize. We can make these 'rouge' cells back into epithelial-like cells and these epithelial cells stay anchored and lose the ability to migrate," says Hari Koul, PhD, investigator at the CU Cancer Center and professor and director of Urology Research at the University of Colorado School of Medicine, the study's senior author.

In fact, the work could have implications far beyond prostate cancer, as increasing evidence points to loss of E-Cadherin as a prerequisite for metastasis in many cancers.

Koul and colleagues first showed that E-Cadherin levels varied directly with the addition or subtraction of SPDEF. Then the group artificially

knocked down E-Cadherin despite the presence of SPDEF and showed that cells remained able to migrate and invade new tissues (SPDEF didn't by itself affect metastasis and was instead dependent on modulating E-Cadherin, which is the driver). The group also showed a one-way switch – SPDEF regulates E-Cadherin, but E-Cadherin expression does nothing to affect levels of SPDEF.

"Taken together, these studies paint a pretty compelling picture of SPDEF working in part through the modulation of E-Cadherin to inhibit prostate cancer metastasis," Koul says. "To the best of our knowledge these are the first studies demonstrating the requirement of SPDEF for expression of E-Cadherin."

Koul says that his group is getting very close to turning off the loss of E-Cadherin in cancer cells by re-arming tumors with the gene that makes SPDEF and my testing small molecules that increase SPDEF in cancer cells.

"This could be a real landmark," Koul says. "We see a prerequisite for metastasis and now we have a very clear picture of how to remove this necessary condition for the most dangerous behavior of prostate cancer."

Provided by University of Colorado Denver