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Major genetic study links liver disease gene to bladder cancer

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A University of Colorado Cancer Center study published today in *Journal of the National Cancer Institute* (with related research being presented this weekend at the American Association for Cancer Research Annual Conference 2014) details the discovery of a new genetic driver of bladder cancer: silencing of the gene AGL.

"We tend to think of cancer resulting from mutations that let genes make things they shouldn't or turn on when they should be quiet. But cancer can also result from loss of gene function. Some genes suppress cancer. When you turn off these suppressors, cancer grows," says Dan Theodorescu, MD, PhD, director of the University of Colorado Cancer Center and the study's senior author.

To discover which genes, when deactivated, might drive bladder cancer, Theodorescu and colleagues turned off genes, one by one, in bladder cancer cell models. Of course, the vast majority of the genes researchers silenced made no difference – they weren't functionally related to tumor growth. But eventually in this genome-wide shRNA screen, Theodorescu and colleagues turned off the gene AGL. The result was dramatic.

"In tumors that were seeded in mouse models, it was only the cells low in AGL that were able to grow," Theodorescu says. Other genes slightly lowered in these successful tumors included INMT, OSR2, ZBTB4 and GPR107, but decrease in AGL far outstripped the others and put AGL at the top of our list for further exploration," says Theodorescu.

Interestingly, this gene is also mutated in a hereditary liver disease called glycogen storage disease 3 (GSDIII). In GSDIII, loss of AGL makes cells unable to efficiently process glycogen and so excess glycogen builds up in the liver.

With the finding of low AGL in liver cancer and related hints from GSDIII, Theodorescu and colleagues turned to the questions of how AGL drives cancer growth, and whether AGL-driven growth is an artifact of lab conditions or is in fact a feature of the human disease.

To evaluate this AGL-driven growth mechanism, the team evaluated all the genes that change in response to turning AGL off in cancer cells. The team saw cells increase production of the enzyme SHMT2, which allows cells to process glycogen into glycine, an amino acid that is known to drive cancer growth. Theodorescu saw the same increase in SHMT2 leading to more glycine in his bladder cancer cells. And previous studies show that glycine is needed for the rapid proliferation of tumor cells.

So as AGL goes down, glycine synthesis goes up and tumors are more able to proliferate.

To discover this mechanism's clinical relevance, Theodorescu and colleagues looked at AGL and SHMT2 expression in 561 samples of human bladder cancer. Sure enough, patients with low-AGL tumors fared worse than patients with high-AGL tumors. The group saw similar effect in mouse models: with AGL silenced, bladder cancer mouse models showed enhanced cell growth and nearly double the rate of new blood vessel formation, which tumors use to supply new tissues with nutrients.

"First, this shows that AGL and SHMT2 levels could be used in bladder cancer prognosis – with lower AGL and higher SHMT2, prognosis is worse and may inform treatment decisions. In addition, these genes may

be targetable players in a pathway that drives cancer. By affecting these levels, we may be able to influence the course of the disease," Theodorescu says.

Provided by University of Colorado Denver