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Researchers identify mechanism used by gene to promote metastasis in human cancer cells

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Virginia Commonwealth University Institute of Molecular Medicine and VCU Massey Cancer Center researchers have discovered how a gene, melanoma differentiation associated gene-9/syntenin (mda-9/syntenin), interacts with an important signaling protein to promote metastasis in human melanoma cells, a discovery that could one day lead to the development of the next generation of anti-metastatic drugs for melanoma and other cancers.

Metastatic disease is one of the primary challenges in cancer therapy. When cancer cells are localized in the body, specialists may be able to surgically remove the diseased area. However, when cancer metastasizes or spreads to sites remote from the primary tumor through the lymph system and blood vessels to new target sites, treatment becomes more difficult and in many instances ineffective.

Previous studies have shown that mda-9/syntenin regulates cell motility and can alter certain biochemical and signaling pathways leading to acquisition of metastatic ability. However, the exact mechanisms involved with these processes have not been well understood until now.

In the study, published online the week of Sept. 29 in the Early Edition of the *Proceedings of the National Academy of Sciences,* researchers report on the molecular mechanisms by which mda-9/syntenin is able to mediate invasion, migration, anchorage-independent growth and

metastasis by physically interacting with c-Src, a key signaling protein involved with tumor cell growth and metastasis.

The team examined human cancer cells in the laboratory using a relevant human melanoma metastasis model and discovered how mda-9/syntenin was able to activate, or switch-on, the expression of c-Src. The expression of c-Src led to an increase in the formation of an active FAK/c-Src signaling complex. According to the researchers, this interaction triggers a signaling cascade resulting in increased cancer cell motility, invasion and metastasis.

"Mda-9/syntenin may represent a potential new molecular target for melanoma therapy that could be used to develop therapeutic reagents for treating this cancer as well as other cancers originating in the breast and stomach," said Paul B. Fisher, M.Ph., Ph.D., professor and chair of the Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine in the VCU School of Medicine.

"By disrupting the interaction between mda-9/syntenin and c-Src, it may be possible to prevent metastasis by blocking those signaling changes necessary for this process," he said.

According to Fisher, using this strategy it may be possible to identify compounds that serve this function and are effective therapeutic molecules for counteracting this final and frequently lethal stage of tumor progression.

The team will conduct further investigations to determine if small molecule drugs can be identified and developed to prevent metastasis by targeting this critical interaction between mda-9/syntenin and c-Src. Further studies are also in progress to determine how general these interactions are in mediating metastasis of other human tumors in addition to melanoma.

Source: Virginia Commonwealth University