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Protein found in heart may be target for colon cancer therapies

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A protein critical in heart development may also play a part in colon cancer progression.

Research led by investigators from Vanderbilt-Ingram Cancer Center and the Vanderbilt Eye Institute suggests that the protein BVES (blood vessel endocardial substance) - which also is key in regulating corneal cells - may be a therapeutic target for halting colon cancer metastasis.

The study, appearing in the October issue of the *Journal of Clinical Investigation*, further suggests that BVES may be important more broadly in many, or most, epithelial cancers.

About 85 percent of cancers originate in epithelial cells that form the body's external and internal linings (such as the skin and the lining of the gastrointestinal tract).

However, the main clinical concern is not the primary tumor, but the potential for that tumor to leave its tissue of origin and spread throughout the body (a process called "metastasis").

A critical step in metastatic progression of epithelial cancers happens when epithelial cells "revert" to a less differentiated state - a process called "epithelial-mesenchymal transition" or EMT.

Ophthalmologist Min Chang, M.D., studies the healing process in the cornea, perhaps the most highly regulated epithelium in the body. From

collaborative studies with David Bader, Ph.D., who discovered BVES and showed its importance in heart development, Chang found that BVES was highly expressed and regulated in corneal cells.

When BVES is disrupted in corneal cells, they become disorganized, almost "cancer-like," noted Chang, an assistant professor of Ophthalmology and Visual Sciences and co-author on the study.

Chang then brought these findings to the attention of colleague Christopher Williams, M.D., Ph.D., assistant professor of Medicine and Cancer Biology and co-author on the study.

"When he described these cells, it sounded a lot like the way cancer cells looked when they were undergoing metastasis," Williams said. "So it seemed reasonable to look in cancer for BVES-dependent phenotypes."

Chang and Williams teamed up with the lab of Daniel Beauchamp, M.D., to assess BVES expression in human colorectal cancers. They found that BVES levels were very low in all stages of colon cancer. They also noted decreased BVES levels in many other types of epithelial cancers (including breast) and in several colorectal cancer cell lines.

To uncover why BVES levels were reduced, the investigators enlisted the help of Wael El-Rifai, M.D., Ph.D., and colleagues. They determined that the BVES promoter (a DNA region that controls gene expression) was heavily modified (methylated), which silenced its expression. In cell experiments, the researchers showed that treating cells with a "demethylating" agent (the drug decitabine, which is currently used to treat myelodysplastic disorders) restored BVES expression. When BVES was expressed in colorectal cancer cell lines, they became more epithelial in nature and their tumor-like characteristics (in cell experiments and in animal models) decreased.

These findings suggest that treatment with agents to increase BVES levels might provide a way to decrease aggressive behaviors of colorectal and other epithelial cancers.

"In cancer, typically the primary tumor doesn't kill you; it's the metastatic disease that proves lethal," said Williams. "So if targeting BVES could interfere with metastasis, that would be very exciting."

The researchers also identified signaling pathways involved in BVES function that may represent other therapeutic targets - and that reveal new insights into the normal biological function of BVES. The findings could have implications in wound healing and other normal functions of epithelial cells, as well as for many types of epithelial cancer.

"We don't think it's just isolated to the colon; it pertains to a broad lot of epithelial cancers," Chang noted. "And that's a lot of cancers."

More information: www.jci.org/articles/view/4422 … 3aac564d108a38a35e37

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