'Jekyll and Hyde'protein both prevents and spreads cancer

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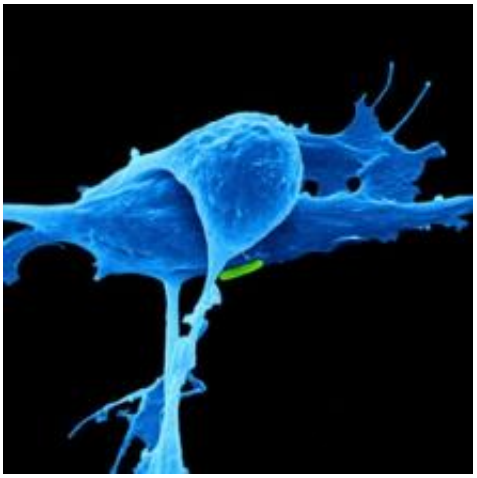

Scottish author Robert Louis Stevenson tapped into primal fears when he penned "Dr. Jekyll and Mr. Hyde," a 19th century novel about a sinister physician, raising the question, "Can evil and good exist in the same person?"

As it turns out, cancer researchers are discovering that "good vs. bad" can also exist in the world of molecular genetics. One example is a protein, transforming growth factor beta (TGF-β) that suppresses tumor progression in pre-malignant cells, can also lead to the spread of cancer. It has been a long-time puzzle how and when TGF-β switches its functional roles from a tumor suppressor to a metastasis promoter. Now,

scientists at The University of Texas MD Anderson Cancer Center believe they have an answer.

A study led by Dihua Yu, M.D., Ph.D., deputy chair of the Department of Molecular and Cellular Oncology at MD Anderson, demonstrates that another protein, known as 14-3-3 zeta, can switch TGF-β from suppressing tumors in pre-cancerous cells to promoting metastasis in breast cancer cells - spreading to the bones by changing the TGF-β's partner proteins.

Yu's results are published in this month's issue of *Cancer Cell*.

"TGF-β has a dual role as both a tumor suppressor in normal and pre-malignant cells, and a metastasis promoter in late-stage cancer," said Yu, who also serves as the Hubert L. & Olive Stringer Distinguished Chair in Basic Science. "The molecular mechanism by which TGF-β switches its role has long been an unsolved mystery for cancer researchers."

Yu and her team may have provided a key to solving that mystery in part by explaining how 14-3-3 zeta destabilizes a key protein, p53, subsequently switching off TGF-β's ability to suppress tumors. In addition, it also promotes the spread of cancer to bones by stabilizing another protein, GLi2.

"TGF-β's known critical role in cancer has led to numerous efforts developing TGF-β inhibitors for anti-cancer therapeutics, but its penchant for both suppressing tumor progression while serving as a springboard for cancer metastasis has been a major obstacle in the development of anti-TGF-β therapies," said Yu. "We have developed a model that proposes that TGF-β's complicated nature may be governed by the cellular effects of SMAD's partner proteins."

SMAD proteins help to regulate the activity of particular genes, as well

as cell growth and division. They, in essence, transmit TGF-β signals from outside the cell to the nucleus, impacting how the cell produces other proteins. SMAD adds to TGF-β's Jekyll and Hyde nature by partnering with the protein p53 to suppress tumors in pre-malignant cells, while helping the protein GLi2 to promote the cancer's spread to bones.

Better definition of this molecular mixing bowl of proteins may lead to new therapies that target TGF-β's critical role in cancer in more effective ways.

"Because TGF-β plays important roles in various physiological functions, it is crucial that we look at how to develop more specific drugs that selectively target TGF-β in cancer so as to discourage its ability to cause metastasis while maintaining its tumor suppression abilities in pre-cancerous cells," said Yu.

Provided by University of Texas M. D. Anderson Cancer Center