A single stem cell mutation triggers fibroid tumors

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Fibroid uterine tumors affect an estimated 15 million women in the United States, causing irregular bleeding, anemia, pain and infertility. Despite the high prevalence of the tumors, which occur in 60 percent of women by age 45, the molecular cause has been unknown.

New Northwestern Medicine preclinical research has for the first time identified the molecular trigger of the tumor --- a single stem cell that develops a mutation, starts to grow uncontrollably and activates other cells to join its frenzied expansion.

"It loses its way and goes wild," said Serdar Bulun, M.D., the chair of obstetrics and gynecology at Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital. "No one knew how these came about before. The stem cells make up only 1 ½ percent of the cells in the tumor, yet they are the essential drivers of its growth."

The stem cell initiating the tumor carries a mutation called MED12. Recently, mutations in the MED12 gene have been reported in the majority of uterine fibroid tissues. Once the mutation kicks off the abnormal expansion, the tumors grow in response to steroid hormones, particularly progesterone.

For the study, researchers examined the behavior of human fibroid stem cells when grafted into a mouse, a novel model initiated by Northwestern scientist Takeshi Kurita, a research associate professor of obstetrics and gynecology. The most important characteristic of fibroid stem cells is

their ability to generate tumors. Tumors originating from the fibroid stem cell population grew 10 times larger compared to tumors initiated with the main cell population, suggesting a key role of these tumor stem cells is to initiate and sustain tumor growth.

"Understanding how this mutation directs the tumor growth gives us a new direction to develop therapies," said Bulun, also the George H. Gardner Professor of Clinical Gynecology.

The paper is published in the journal *PLoS ONE*. Masanori Ono, M.D., a post-doctoral student in Bulun's lab, is the lead author.

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