Understanding culprits behind fibroid tumors

October 14 2013

(Medical Xpress)—Tremendous progress has been made in understanding how uterine fibroid tumors—the most common tumor in women – start and grow. A new paper in the *New England Journal of Medicine* synthesizes the latest research on the role of the hormone progesterone, stem cells and tumor mutations that together offer a new direction for research and drug development.

"These findings represent a paradigm shift in how we will approach new treatments," said article author Serdar Bulun, M.D., the chair of obstetrics and gynecology at Northwestern University Feinberg School of Medicine and Northwestern Memorial Hospital.

Bulun's research about how progesterone and the tumor's stem cells engineer its uncontrolled growth largely shapes the new thinking about these tumors.

"This will shift the way people think about fibroids in research and drug development," Bulun said. "They will now target this crosstalk between stem cells, growth factors and progesterone and specifically target only 1 to 5 percent of all cells in a fibroid. In the past, it was a shotgun approach when we were trying to shrink these tumors by attempting to affect 100 percent of the cells indiscriminately; then the treatment strategy gets diluted and causes severe side effects such as hot flashes and bone loss. If you target the tumor stem cell population in a laser sharp manner, then it is much more likely to be successful with minimal side effects."

By the time women reach 50 years of age, nearly 70 percent of white women and more than 80 percent of black women will have had at least one fibroid; severe symptoms develop in 15 to 30 percent of these women. Uterine fibroids in black women are significantly larger at diagnosis than those in white women, are diagnosed at an earlier age, and are characterized by more severe symptoms and a longer period of sustained growth.

Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterineartery embolizations and high-intensity focused ultrasound procedures are performed annually in the United States to remove or destroy uterine fibroids. The annual economic burden of these tumors is estimated to be between $5.9 billion and $34.4 billion.

In 2009, Bulun and colleagues, Julie Kim, Debabrata Chakravarti, Erica Marsh, Takeshi Kurita, and JianJun Wei from Northwestern, and Romana Nowak from University of Illinois at Urbana-Champaign received a P01 grant to sustain the only National Institutes of Health supported comprehensive uterine fibroid research center in the country. In June 2010, scientists at Feinberg, led by Kurita, redefined the roles that estrogen and progesterone play in a discovery that set the stage for major findings to come. That paper, published in *Endocrinology*, provided proof that estrogen acts in a permissive rather than causative role in uterine fibroid formation. The sex steroid works to prepare uterine tissue to respond to progesterone and progesterone receptor, and it is these hormones that promote tumor growth.

"By identifying a plausible mechanism of tumor growth, our work triggered the field to develop a drug that has already been approved in the European Union and Canada," Bulun said. "Two papers published in 2012 in the *New England Journal* verified the role of progesterone and demonstrated the efficacy of an anti-progesterone drug to treat fibroids."

If the drug is introduced in the U.S. in the near future, as Bulun suspects, it will mark the first time since the early '90s that a new drug will be offered to fight uterine fibroids.

Although the cellular origin of uterine fibroids remains unknown, several observations support the notion that each fibroid originates from the transformation of a single somatic, or adult, stem cell.

In a 2011 paper published in *Science*, a somatic single-gene defect was found in a majority of uterine fibroid tumors. The group of mutations affects the gene encoding MED12, and though not well understood, the gene is mutated in 80 percent of all fibroids.

The following year, Bulun's lab revealed in a *PLOS ONE* publication that the growth of human fibroid tumors, dependent on estrogen and progesterone, also require the presence of these stem cells, which make up just one percent of the tumor. Most importantly, Bulun's group reported that fibroid stem cells, but not the stem cells from the surrounding uterine tissue, carried MED12 mutations.

Bulun thinks scientists will now seek to develop treatment strategies that target the small stem cell population present in uterine fibroids in an effort to develop new treatment options.

Provided by Northwestern University