PI3K/mTOR pathway proteins tied to poor prognosis in breast cancer

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Four proteins involved in translation, the final step of general protein production, are associated with poor prognosis in hormone-receptor-positive breast cancer when they are dysregulated, researchers reported at the AACR Annual Meeting 2012.

All of the aberrantly activated translational proteins are regulated by the PI3K/mTOR molecular signaling pathway, which has been implicated in development and progression of several cancers.

More recently, mTOR activation has been tied to resistance to standard endocrine therapy in estrogen-receptor positive breast cancer, said Funda Meric-Bernstam, M.D., professor in MD Anderson's Department of Surgical Oncology, who presented the research at AACR.

"These data underline the importance of the PI3K/mTOR pathway in hormone receptor-positive breast cancer and suggest potential new prognostic factors and therapeutic targets," said Meric-Bernstam, who also is medical director of MD Anderson's Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy.

Two drugs that inhibit mTOR, everolimus and temsirolimus, are approved for treatment of certain cancers and there are dozens of other agents in clinical trials, she said.

Cancer cells rely on increased protein synthesis

Genes express messenger RNA, which is in turn processed through a cell's ribosomes to produce a specific protein, a step called translation.

"Cancer cells need a lot of protein synthesis to grow and survive," Meric-Bernstam said. She and colleagues systematically analyzed several major translation-regulating proteins in tumors from 190 patients with stage 1 to stage 3 hormone receptor-positive breast cancer. Median follow-up was 96 months.

They found four aberrations that were predictors of overall survival. They remained significant even after multivariable analysis accounting for other factors such as age and node-positive status that also affect survival. They are:

- Increased phosphorylation of ribosomal protein S6 (pS6) and of translation initiation factor 4E-binding protein 1 (p4E-BP1).
- Increased expression of eukaryotic elongation factor 2 kinase (eEF2K).
- Decreased expression of programmed cell death protein 4 (pdcd4).

Their findings, if validated by additional studies, could lead to markers that help select patients who may have a high risk of relapse if treated with traditional endocrine therapy alone and identify those who might benefit from an additional targeted therapy, Meric-Bernstam noted.

Results from a major phase III clinical trial presented at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium showed that the mTOR inhibitor everolimus increased progression-free survival when combined with the hormonal therapy exemestane to treat resistant hormone receptor-positive breast cancer.

"As we understand how to select patients better we'll be able to more efficiently use these targeted therapies to improve outcomes for breast cancer patients," Meric-Bernstam said.

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