Researchers identify signaling protein for multiple myeloma

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Researchers at Emory University's Winship Cancer Institute are the first to discover a mechanism that plays a critical role in the multiple myeloma cell cycle and survival. Their research may result in identification of a new therapeutic target for treating multiple myeloma.

The results of the study appear in the September issue of *Cancer Cell*. Jing Chen, PhD, assistant professor of hematology and oncology at Emory Winship and a Georgia Cancer Coalition Distinguished Cancer Scholar, is senior author on the paper. Sumin Kang, PhD, a postdoctoral fellow at Emory Winship, is the paper's first author.

Multiple Myeloma is among the most common hematologic malignancies in patients over 65. About15 percent of multiple myeloma patients harbor a genetic abnormality called "t(4;14) chromosomal translocation" that causes over-expression of a tyrosine kinase called fibroblast growth factor receptor 3 (FGFR3).

Tyrosine kinases are molecules that act as biological switches inside cells, regulating processes including cell division and growth. Abnormal kinases have been identified as a driving force in many forms of cancer.

"We are interested in how FGFR3 mediates transforming signals," says Dr. Chen. "We wanted to know which protein factors in cells are activated by FGFR3 and then transform normal cells to highly malignant cells. We identified Ribosomal S6 kinase 2 (RSK2), which is a protein factor that mediates signaling in cells as critical in downstream signaling

of FGFR3 in myeloma cells."

Dr. Chen and his colleagues are the first to discover a mechanism to "turn-on" RSK2 by FGFR3. FGFR3 impacts downstream proteins through phosphorylation at special "tyrosine" sites.

"We found that FGFR3 directly phosphorylates RSK2, which is a critical step in the process to activate (turn-on) RSK2," says Dr. Chen.

The researchers observed that elimination of RSK2 proteins or shutting down RSK2 activity blocks FGFR3 transformation signaling in myeloma cells. This means FGFR3 requires RSK2 to transform normal cells.

"This is a beautiful model," says Dr. Chen. "We are able to mark the connection between the oncogenic FGFR3 and its downstream protein kinase RSK2, which plays a critical role in regulation of cell cycle and survival. These findings extend our understanding of pathogenesis of multiple myeloma in a signaling basis."

Collaborators on the project include Roberto Polakiewicz, PhD, and Ting-Lei Gu, PhD, both of Cell Signaling Technologies (CST), developers of the "PhosphoScan" technology, which enables investigators to identify hundreds to thousands of phosphorylated sequences and observe the global state of protein tyrosine phosphorylation in cells and tissues.

"Using this technology," says Dr. Chen, "we identified RSK2 as a critical downstream signaling protein effector of FGFR3 in myeloma cells." Other authors include researchers from the University of California at San Francisco, Harvard Medical School, Mayo Clinic and Novartis Pharma AG.

Dr. Chen and his colleagues also tested a drug called fmk that was

designed by co-author Jack Taunton, PhD, at UCSF to specifically target RSK2 in treatment of human malignant myeloma cells from laboratory culture or primary samples from multiple myeloma patients, and saw that fmk effectively kills t(4;14) myeloma cells with abnormal over-expression of FGFR3.

“This study shows the potential utility of drugs that block the downstream effectors of mutant tyrosine kinases, and that these drugs are opening more doors to treating hematologic malignancies and cancers," explains Dr. Chen. In addition to the t(4;14) in multiple myeloma that is caused by abnormal over-expression of FGFR3, abnormality of FGFR3 has also been identified in human bladder and cervical cancers. The findings suggest, the authors write, that targeting RSK2 with RSK inhibitors such as fmk may be effective in treating t(4;14) multiple myeloma, as well as other diseases and cancers where mutant FGFR3 is the culprit.

Source: Emory University