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TJP1 protein may identify multiple myeloma patients most likely to benefit from proteasome inhibitors

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A gene known as TJP1 (tight junction protein 1) could help determine which multiple myeloma patients would best benefit from proteasome inhibitors such as bortezomib, as well as combination approaches to enhance proteasome inhibitor sensitivity, according to a study led by The University of Texas MD Anderson Cancer Center.

Multiple myeloma is a cancer that forms from white blood cells found in the bone marrow, normally vital to producing antibodies and maintaining a healthy immune system. It is the second most common type of blood cancer.

"Proteasome inhibitors form the cornerstone of our standard therapy for multiple myeloma. However, no biomarkers have been clinically validated that can identify patients most likely to respond to this treatment," said study lead Robert Orlowski, M.D., Ph.D., chair ad interim of Lymphoma/Myeloma. "Our findings provide a rationale for use of TJP1 as the first biomarker to select patients who are most and least likely to benefit from proteasome inhibitors."

The research team's findings are published in the April 28 online issue of *Cancer Cell*.

TJP1 has not previously been known to play any role as a mediator of proteasome inhibitor sensitivity in multiple myeloma. Orlowski's group

showed that TJP1 modulated signaling through a pathway involving EGFR, JAK1, and STAT3. The study findings supported the hypothesis that plasma cells which express low TJP1 levels have both high EGFR/JAK1/STAT3 activity and proteasome content.

"Therefore, these plasma cells were resistant to proteasome inhibitors," said Orlowski. "Moreover, they demonstrated a previously unknown role for EGFR signaling in myeloma, and for STAT3 in controlling the level of proteasomes in cells, and therefore the cell's ability to break down proteins.

The team observed that patients whose myeloma cells expressed low TJP1 levels were significantly less likely to achieve a response or benefit from bortezomib.

"This study allows us to identify promising future directions to overcome proteasome inhibitor resistance in patients with high signaling through EGFR/JAK1/STAT3 pathway by offering combination therapies such as bortezomib with either the EGFR inhibitor erlotinib, or a JAK1 inhibitor such as ruxolitinib," said Orlowski.

The research was part of MD Anderson's SPORE in Multiple Myeloma, and also the Moon Shots Program aimed at accelerating the conversion of scientific discoveries into clinical advances and significantly reducing cancer deaths.

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