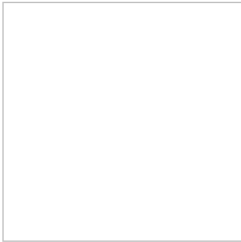


CREB1 INHIBITION DISRUPTS CANCER CELLS’ PROTECTIVE MECHANISMS IN MULTIPLE MYELOMA

A study by researchers at the OSUCCC – James highlights the molecular mechanisms of multiple myeloma (MM) cell survival under stress and suggests new therapeutic strategies for patients with this currently incurable blood cancer.



Published in the journal [Cell Death & Disease](#), the study – which was supported in part by funds from [Pelotonia](#) – was led by corresponding author **Francesca Cottini, MD**, assistant professor in the Division of Hematology at Ohio State and member of the Leukemia and Hematologic Malignancies Program at the OSUCCC – James.

The researchers state that current proteasome inhibitor drugs such as bortezomib and carfilzomib have greatly improved outcomes for patients with MM, but most patients develop resistance after two to five years. Newer biologics (e.g., teclistamab and daratumumab) offer different approaches but make patients highly prone to infections, including pneumonia, and are thus particularly risky for older patients. Stem cell transplantation to induce deeper remission is a high-stakes procedure, and many patients don’t qualify.

In time, all MM patients relapse under the current treatment paradigm, but Dr. Cottini’s team is studying cancer cell inhibition from a novel perspective in hopes of overcoming limitations of current therapies.

In 2022, they demonstrated that the *CD56* gene drives *CREB1* gene pro-survival activation in MM cells. In the current study, they elucidated the mechanism of action (MOA) for a chain of events from *CD56* to *CREB1* to rapamycin (mTOR) activation and how it protects MM cells against stressors that otherwise would lead to autophagy (a natural process that removes damaged cells and regenerates healthier cells).

As proof of the MOA, and to set the stage for drug development, they found a compound called 666-15 that would inhibit *CREB1*, thereby helping to disarm the cancer cells.

Stress-adaptation pathways

The researchers explain that cancer cells live in conditions of hypoxia (oxygen deficiency), nutrient limitation, oxidative stress, endoplasmic reticulum (a membrane system within cells) stress and chemotherapy exposure. MM cells endure particularly high oxidative stress, as well as proteotoxic stress.

To fight this, the scientists write, the cells meticulously regulate the proteostasis (protein) network, helping prevent the accumulation of misfolded proteins and the resulting cytotoxic protein aggregation that threaten their survival. This adaptation involves reliance on the proteasome and autophagosome systems and overactivation of the mTOR pathway. In concert, these and related defenses help the cell better survive proteotoxic stress and resist both apoptosis (natural cell death) and anticancer therapy.

The counterattack

Using *in silico* data from patients with MM, Dr. Cottini’s team sought a durable means of breaking down the MM cells’ ability to adapt to stressors. Knowing that high *CREB1* levels are associated with MM cell survival, they explored how high *CREB1* expression activates their stress endurance, hypothesizing that *CREB1* could be implicated in the regulation of oxidative stress and proteostasis in MM cells.

Targeting mTOR or chaperone proteins has been studied in preclinical models and clinical trials, but resistance develops. The question became: Does targeting the pathway upstream from mTOR produce better results? Their work first confirmed that patients with high *CREB1* expression have greater activation of gene sets associated with endurance of stress. They then confirmed that *CREB1* activates the mTOR pathway, halting autophagy and directly binding to the promoter of *NRF2* and *PERK*, which are modulating genes involved in oxidation and protein stress adaptation.

Then, using the compound 666-15, a potent, cell-permeable small molecule *CREB1* inhibitor, they demonstrated that inhibiting *CREB1* resulted in increased reactive oxygen species levels, triggering significant autophagy and apoptosis. They also showed, for the first time, that inhibiting the *TXNIP* gene is toxic to MM cells, interfering with the protection and repair of unfolded protein response and autophagy.

In addition, they showed that the combined inhibition of *CREB1* and *TXNIP* is extremely toxic to MM cells, reducing their adaptation to stress by around 50%.

“Thus, our data highlight the essential roles of *CREB1* and *TXNIP* in MM cell survival under chronic stress, providing new insights into MM pathophysiology and novel therapeutic strategies for patients with high-risk disease,” Dr. Cottini says, adding that she is looking at different ways to target the same proteins or pathways and is studying other proteins that may drive durable responses.

Her team’s work was sponsored by the International Myeloma Society and the Paula and Rodger Riney Foundation Translational Research Award, the Multiple Myeloma Research Foundation, Pelotonia, the Elsa U. Pardee Foundation, The Ohio State University College of Medicine and the National Cancer Institute.

Other members of Dr. Cottini’s team who were co-authors of this study include **Ruchi Kudalkar, Jonathan Altom, Joshua Galloway, Vincent Manning** and **Sara Taranto, PhD**.

