First-in-class drug ONC201 shows potential for some blood cancers

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ONC201, an anti-cancer drug that triggers cell death in various tumor types, may have clinical potential for some blood cancers including mantel cell lymphoma (MCL) and acute myeloid leukemia (AML), according to a recent clinical study.

A research team led by Michael Andreeff, M.D., Ph.D., professor of Leukemia at The University of Texas MD Anderson Cancer Center, found that ONC201, which is in early clinical trials, caused cell death even when a crucial protein known as p53 is mutated or deleted entirely. This dysfunction occurs in more than half of malignancies and can promote malignant characteristics of cancers as well as resistance to standard chemotherapy, raising an urgent need for novel therapeutic solutions.

The study results are published in the Feb. 16 online issue of *Science Signaling*.

ONC201 is a first-in-class drug being clinically developed by Oncoceutics Inc. and MD Anderson through an alliance formed in January 2015. The drug is of interest due to its ability to kill cancer cells without harming healthy cells. Previously, Andreeff and others conducted extensive pre-clinical studies of ONC201.

"The clinical challenge posed by p53 abnormalities in blood malignancies is that therapeutic strategies other than standard chemotherapies are required," said Andreeff. "We found that ONC201 caused p53-independent cell death and cell cycle arrest in cell lines and in lymphoma and acute leukemia patient samples."

The patient samples included those that demonstrated genetic abnormalities linked to a poor prognosis or cells that developed resistance to the drugs ibrutinib and bortezomib commonly used for lymphoma and multiple myeloma patients. Additionally, mice studies revealed that ONC201 caused cell death in AML and leukemia stem cells but appeared to spare normal bone marrow cells.

ONC201 increased the translation of the stress-induced protein ATF4 through stress signals which are similar to those caused by cellular responses known as UPR (unfolded protein response) and ISR (integrated stress response). Every cellular protein must be properly folded for cells to survive. UPR is the major response against unfolded proteins, and prolonged or excess UCR can eventually cause cell death. Using similar mechanisms, nutrient deprivation and viral infection can cause ISR. ATF4 is commonly induced in these responses and by ONCO201 treatment. ATF4 has the ability to turn specific genetic instructions on and off.

"This increase in ATF4 in ONC201-treated hematopoietic cells promoted cell death," said Andreeff. "However, unlike with UPR and ISR, the increase in ATF4 in ONC201-treated cells promoted was not regulated by standard molecular signaling, indicating a novel mechanism of stressing cancer cell to death regardless of p53 status. There is clear evidence that ONC201 has clinical potential in hematological malignancies. Clinical trials in leukemia and lymphoma patients have recently been initiated at MD Anderson."

More information: J. Ishizawa et al. ATF4 induction through an atypical integrated stress response to ONC201 triggers p53-independent apoptosis in hematological malignancies, *Science Signaling* (2016). DOI: 10.1126/scisignal.aac4380

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