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Hard-to-treat Myc-driven cancers may be susceptible to drug already used in clinic

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Drugs that are used in the clinic to treat some forms of breast and kidney cancer and that work by inhibiting the signaling molecule mTORC1 might have utility in treating some of the more than 15 percent of human cancers driven by alterations in the Myc gene, according to data from a preclinical study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"More than 1 million people diagnosed with cancer each year have a tumor driven by alterations in the Myc gene," said Grant A. McArthur, M.D., Ph.D., professor of translational research at the Peter MacCallum Cancer Centre in Melbourne, Australia. "However, it has proven impossible to develop drugs that effectively target Myc.

"One of Myc's functions is to regulate cell growth. Because mTORC1 is also a regulator of cell growth, we hypothesized that inhibiting mTORC1 with the drug everolimus might suppress Myc-driven tumor initiation and growth."

McArthur and his colleagues tested their hypothesis in a mouse model of Myc-driven lymphoma and found that treatment with everolimus provided strong protection against disease: only four of 33 mice treated with everolimus developed lymphoma, while 22 of 34 mice treated with placebo developed the disease.

In addition, treatment with everolimus led to tumor regression and significantly improved survival compared with placebo in mice with

established lymphomas. However, all of these mice eventually relapsed as a result of the growth of lymphoma cells resistant to the effects of everolimus.

"These data confirmed our hypothesis that mTORC1 inhibition could suppress Myc-driven tumor initiation and growth," said McArthur. "The surprise was found in how mTORC1 inhibition led to tumor regression. We had expected that it would trigger cancer cells to die by a cellular process known as apoptosis, but we found that this was not the case."

Detailed analysis of the tumors indicated that everolimus caused tumor regression by inducing cellular senescence.

According to McArthur, normal cells protect themselves when cancer-driving genes are switched on is by entering a state called senescence. When cancers develop, they have found ways to overcome this safeguard. "Our data indicate that one way in which cancers bypass senescence, in particular senescence induced by Myc, is through a signaling pathway involving mTORC1," he said.

Resistance to everolimus treatment in mice with established lymphomas was associated with loss of the function of p53, a protein known to help suppress tumor formation and growth.

"The loss of effectiveness of everolimus therapy against lymphoma cells deficient in p53 function has important clinical implications," said McArthur. "Everolimus could be a useful new string to the bow for clinicians treating patients with Myc-driven cancers, in particular B cell lymphomas, but that it would be helpful only to those patients with functional p53."

Provided by American Association for Cancer Research