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Inhibition of CDK4 might promote lymphoma development, progression

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Anticancer agents that inhibit tumor growth by targeting a regulatory protein called CDK4 might actually promote the development and progression of certain B-cell lymphomas, according to a new study led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The study indicates that inhibiting CDK4, a regulator of the cell cycle, promotes genetic instability and the development or progression of B-cell lymphomas that are driven by the MYC oncogene.

The research suggests that CDK4 inhibitors, which are now in clinical testing, should be used cautiously, particularly in patients with B-cell lymphomas. The findings also raise the possibility that these inhibitors work through off-target effects and require further investigation.

The study is published in *The Journal of Clinical Investigation*.

"Anti-CDK4 strategies are being widely tested as broad-spectrum anticancer therapies," says study leader Xianghong Zou, PhD, assistant professor of medicine and a member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program. Zou's collaborators on the research included John Cleveland, PhD, professor and chair of cancer biology at The Scripps Research Institute.

"Our findings indicate that anti-CDK4 strategies must be carefully

tailored because they might have unexpected lymphoma-promoting effects," Zou says.

"It was quite striking," he adds. "Silencing Cdk4 in our mouse model and in human B-cell lymphoma cells had the opposite effect of small-molecule inhibitors that are touted as selective inhibitors of CDK4 and CDK6," he says.

"Given that these agents have undergone limited profiling, it might be that these agents inhibit kinases other than CDK4, and that in lymphoma cells they promote critical factors that support cell growth and survival."

For this study, Zou and his colleagues used a mouse model of MYC-driven B-cell lymphoma they had developed earlier, and human cell lines of Burkitt and other non-Hodgkin lymphomas.

Key technical findings include:

- Although CDK4 functions as an oncogene in breast and other cancers, loss of CDK4 can greatly promote cancer onset and growth in a model of MYC-driven B-cell lymphoma and in human B-cell lymphoma cells;
- The lymphoma-promoting effects of the experimental CDK4 deficiency were associated with dysregulation of a gene pathway that leads to genomic instability;
- CDK4 deficiency leads to lymphomas with major genomic alterations that are associated with the dysregulation of genes that are known to promote cancer.

More information: www.jci.org/articles/view/63139