AZD6738 found to slow some types of children's tumor growth in mouse models

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(Medical Xpress)—A team of researchers from the U.S., Germany and Japan has found that the chemical AZD6738 was able to slow some childhood type tumor growths in mouse models. In their paper published in the journal *Science Translational Medicine*, the group describes why the application of the chemical represents an entirely new way to treat

tumor growth in children.

Prior research has shown that cancer in children is very seldom the same as cancer in adults—in many cases, tumors that grow in children differ markedly from tumors that grow in adults which means they require completely different types of treatment. Unfortunately, treatments for childhood tumors has progressed at a much slower pace than for adults. Just four of them, for example, have been approved for use in the U.S. over the last 25 years. One of the main ways to treat adult tumors is to apply chemicals that serve to actively reduce tumor size, an approach that has not worked well with children. To get around that problem, the researchers with this new effort have been studying a chemical that has shown an ability to stop tumor growth by preventing tumor cells from repairing their DNA.

The researchers began by noting that prior research had shown that many types of childhood tumors rely on a DNA pathway called nonhomologous end joining (NHEJ) to survive. That led them to search for a chemical that would disrupt the pathway, preventing the cell from repairing its own DNA. Such tumors, the researchers noted, appear to depend on NHEJ to help them overcome problems with handling the excess amounts of an enzyme called PGBD5 they produce.

After finding that applying the chemical AZD6738 to tumor cells directly prevented them from growing, the team then began testing it in mouse models (mice with human tumor cells implanted in them). They report that doing so caused two types of tumors to stop growing but did not work against two others. While promising, the researchers acknowledge that the chemical is not likely to represent a means for destroying tumors in human patients even if it were to pass clinical trials. It stops growth but does not decrease tumor size. But that would of course still be a far better outcome for treating patients who have no other options.

More information: Anton G. Henssen et al. Therapeutic targeting of PGBD5-induced DNA repair dependency in pediatric solid tumors, *Science Translational Medicine* (2017). DOI: 10.1126/scitranslmed.aam9078

Abstract

Despite intense efforts, the cure rates of childhood and adult solid tumors are not satisfactory. Resistance to intensive chemotherapy is common, and targets for molecular therapies are largely undefined. We have found that the majority of childhood solid tumors, including rhabdoid tumors, neuroblastoma, medulloblastoma, and Ewing sarcoma, express an active DNA transposase, PGBD5, that can promote site-specific genomic rearrangements in human cells. Using functional genetic approaches, we discovered that mouse and human cells deficient in nonhomologous end joining (NHEJ) DNA repair cannot tolerate the expression of PGBD5. In a chemical screen of DNA damage signaling inhibitors, we identified AZD6738 as a specific sensitizer of PGBD5-dependent DNA damage and apoptosis. We found that expression of PGBD5, but not its nuclease activity–deficient mutant, was sufficient to induce sensitivity to AZD6738. Depletion of endogenous PGBD5 conferred resistance to AZD6738 in human tumor cells. PGBD5-expressing tumor cells accumulated unrepaired DNA damage in response to AZD6738 treatment and underwent apoptosis in both dividing and G1-phase cells in the absence of immediate DNA replication stress. Accordingly, AZD6738 exhibited nanomolar potency against most neuroblastoma, medulloblastoma, Ewing sarcoma, and rhabdoid tumor cells tested while sparing nontransformed human and mouse embryonic fibroblasts in vitro. Finally, treatment with AZD6738 induced apoptosis and regression of human neuroblastoma and medulloblastoma tumors engrafted in immunodeficient mice in vivo. This effect was potentiated by combined treatment with cisplatin, including substantial antitumor activity against patient-derived primary neuroblastoma xenografts. These findings delineate a therapeutically

actionable synthetic dependency induced in PGBD5-expressing solid tumors.