

Novel enzyme inhibitor paves way for new cancer drug

Combining natural organic atoms with metal complexes, scientists at The Wistar Institute have developed a new type of enzyme inhibitor capable of blocking a biochemical pathway that plays a key role in cancer development.

Based on studies in human melanoma cells, the research paves the way for developing new ways to treat cancer by dampening the overactive enzyme activity that leads to uncontrolled tumor growth.

Details of the study, to be published in the May 16 issue of the journal *ACS Chemical Biology*, show how small-molecule inhibitors can be designed to target a family of signaling proteins, called phosphatidylinositol-3-kinases, or PI3Ks.

“The PI3K pathway has been called the most mutated pathway in human cancer,” says Ronen Marmorstein, Ph.D., a professor in the Gene Expression and Regulation Program at Wistar and senior author of the study.

PI3Ks are a family of lipid kinases – enzymes that transfer a phosphate group to an important signaling molecule in the cell called a lipid. They play a key role in a wide range of cellular functions, including cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. Lipid kinases also drive cell division by modifying fatty acid molecules and directing cells to grow, change shape and move.

Kinases have been the focus of drug development strategies for years, with some protein kinase-inhibiting compounds, such as Gleevec, already being used clinically to inhibit tumor growth. Though pharmaceutical companies have a keen interest in developing similar types of inhibitors for lipid kinases, targeting these enzymes remains a challenge.

The problem is, the drugs often lack specificity, Marmorstein says. Such broad-spectrum compounds, which inhibit many different but related kinases, inevitably cause side effects and are therefore poor drug candidates. For these reasons, none of the PI3K-inhibitors developed to date have proven useful as therapeutic agents, he says.

To overcome this hurdle and develop an inhibitor with greater specificity, and therefore greater potential as a drug candidate, Marmorstein and his colleagues set out to create a lipid kinase inhibitor using a metal complex in its structure.

Though most protein inhibitors are created using purely organic atoms—such as carbon, nitrogen, oxygen and sulfur—adding a metal to the mix allows one to create compounds that are otherwise impossible to make with a purely organic toolbox, Marmorstein says.

“The metal not only lends a structural support to the inhibitor but also provides the ability to form and accept a wider range of ligands, or chemical building blocks, to increase kinase selectivity,” he says.

Working with Eric Meggers of the University of Pennsylvania (now at the Philipps-Universität Marburg in Germany), who has developed organometallic enzyme inhibitors for other types of kinases, the scientists combined traditional organic compounds with the metal Ruthenium to create a novel scaffold, the platform on which the inhibitor was constructed.

After screening a general organometallic library of compounds designed by Meggers to identify potential agents to inhibit PI3K, the scientists identified a protein kinase inhibitor known as DW2.

The scientists then used X-ray crystallography to determine the three-dimensional structure of PI3K bound to DW2, using the structure as a “starting point” to fashion more effective PI3K inhibitors.

Based on what they had observed in their structural studies, the scientists were able to make several changes to the inhibitor to prepare a more potent and selective agent, Marmorstein says.

To determine how well their new inhibitor, called E5, could selectively target PI3K lipid kinases, the researchers tested the agent on five different human protein kinases representing four kinase families. The study showed E5 selectively targeted the PI3K lipid kinases.

In collaboration with Meenhard Herlyn, D.V.M., D.Sc., at the Wistar Institute, the Marmorstein group then tested the effectiveness of the agent using melanoma cell cultures. Melanoma was used as a model system for the study because the signaling pathway regulated by PI3K is highly mutated in melanoma, Marmorstein says.

In addition to PI3K, the PI3K signaling pathway includes another kinase called AKT, and a phosphatase, PTEN, which serves as a tumor suppressor.

“What you will often find is that one of those three proteins, and sometimes others, are mutated in cancer,” Marmorstein says.

Studies with human melanoma cells showed that E5 blocked AKT activity, thereby inhibiting the growth of cells. Further studies in 3D cultures of melanoma cells showed the agent also prevented melanoma cell invasion.

“What we’ve shown is that our inhibitor can find the kinase that it’s designed to inhibit without inhibiting other kinases, which could produce unwanted side effects,” he says.

Marmorstein says the group plans to improve upon the E5 compound by creating organometallic inhibitors that target other isoforms, or types, of PI3K. The PI3K family of kinases includes four types: alpha, beta, delta and gamma. Each type is associated with particular biological pathways and performs various functions in the cell.

Though some of the PI3K types are associated with cancer, others are not. The trick to building inhibitors with low side effects and toxicity is to create inhibitors that knock out the troublesome isoforms without disrupting the other types, Marmorstein says

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