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New class of antiangiogenesis drugs identified

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Massachusetts General Hospital (MGH) researchers have discovered the first of an entirely new class of antiangiogenesis drugs – agents that interfere with the development of blood vessels. In a report in *Proceedings of the National Academy of Sciences Early Edition*, the investigators describe how a compound derived from a South American tree was able, through a novel mechanism, to interfere with blood vessel formation in animal models of normal development, wound healing and tumor growth.

"Most of the FDA-approved antiangiogenesis drugs inhibit the pathway controlled by vascular endothelial growth factor or VEGF, which directly stimulates blood vessel development," says Igor Garkavtsev, MD, PhD, of the Steele Laboratory for Tumor Biology at MGH, lead author of the study. "Although these drugs have become standard treatments for several types of cancer, they only provide modest benefit in terms of extending patient survival, so more effective drugs targeting tumor vasculature are needed."

While tumors need to generate and maintain their own blood supply to keep growing, tumor vasculature tends to be highly disorganized, which interferes with the effectiveness of traditional treatments like radiation and chemotherapy. Drugs that target the VEGF pathway can "normalize" tumor vasculature and improve the effectiveness of other therapies, but in addition to their limited effect on patient survival, such agents also can generate resistance or have toxic effects.

In their search for drugs that block blood vessel growth in different ways, Garkavtsev and his colleagues focused on pathways involved with the adhesion of endothelial cells that line blood vessels to the outer vessel wall. Appropriate cellular adhesion is essential to blood vessel function, and cells lining the tangled vessels characteristic of tumors often exhibit altered adhesion. Using a novel two-step strategy, the team first screened 50,000 compounds to find those affecting cellular adhesion and then analyzed identified compounds for toxicity and for their effects on actin, a protein essential to cellular structure.

One of two compounds identified by this process was dehydro-alpha-lapachone (DAL), derived from Tabebuia avellanedae, a tree native to Argentina and Brazil. Since DAL has structural similarities to another agent with antitumor activities and did not appear to be toxic, it was chosen for further investigation. The researchers first showed that DAL administration interfered with blood vessel formation in zebrafish, both during embryonic development and wound healing. They then found that it reduced the vascular density of tumors implanted in mice and, with daily treatment, significantly reduced tumor growth with no signs of toxicity.

Experiments with endothelial cells from human umbilical veins revealed that DAL administration altered the size and shape of the cells by changing the organization of the actin cytoskeleton; blocked formation of new vascular networks and reorganized existing networks; and interfered with the movement of cells required for wound healing. Further investigation found that DAL produces these effects by decreasing the activity of Rac1, a protein known to be important to cellular adhesion and cytoskeletal organization.

"This work is the first to discover the antivascular effects of DAL and its target Rac1, and our data strongly suggest that DAL promotes Rac1 degradation," says Rakesh Jain, PhD, director of the Steele Lab and

senior author of the study. "DAL has the potential to improve treatment of many types of cancer and of other diseases characterized by abnormal blood vessels." Jain is the Cook Professor of Radiation Oncology (Tumor Biology) and Garkavtsev is an assistant professor of Radiation Oncology at Harvard Medical School

Provided by Massachusetts General Hospital