Generic drug may improve the effectiveness of cancer nanotherapies

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Low doses of an inexpensive, FDA-approved hypertension medication may improve the results of nanotherapeutic approaches to cancer treatment. In a report in the early edition of *Proceedings of the National Academy of Sciences*, Massachusetts General Hospital (MGH) investigators describe experiments showing that the generic drug losartan, by modifying the network of collagen fibers that characterizes most solid tumors, improved the effectiveness of two nanotherapeutics against several types of cancer.

"By 'normalizing' the abnormal extracellular matrix of tumors, which keeps many therapies from reaching cancer cells, losartan improved both the delivery and efficacy of cancer nanotherapies," says Rakesh Jain, PhD, director of the Steele Laboratory for Tumor Biology at MGH and senior author of the study. "We also found that this effect occurs at much lower doses than those used to manage hypertension."

Jain's team focuses on understanding how the physical and physiologic properties of tumors - including their erratic blood supply and network of disorganized, fibrous tissues - inhibit the delivery of anticancer drugs and on developing strategies for getting around those barriers. His team investigated whether losartan might help nanotherapeutics penetrate tumors because, in addition to its antihypertension properties, the drug is known to reduce the formation of excess fibrous tissue that can accompany heart and kidney disease and to normalize connective tissue in the genetic disorder Marfan syndrome. Although the particles that deliver nanotherapies are extremely small, they are still much larger than the extracellular spaces within most solid tumors.

In a series of experiments, the MGH investigators confirmed that low doses of losartan could inhibit the formation of collagen by tumor-associated fibroblasts in culture and within tumors implanted in mice. Losartan also improved the distribution within tumors of fluorescent nanoparticles injected either intravenously or directly into the tumors. Experiments with two nanotherapeutics - liposomes containing the chemotherapy drug doxorubicin and a virus designed to infect and destroy cancer cells - showed that combining each treatment with losartan significantly reduced the size or delayed the growth of implanted tumors.

"We know that losartan is safe for clinical use with minimal side effects, and since it is a generic drug, it is very inexpensive," says Yves Boucher, PhD, associate biologist in the Steele Laboratory and co-senior author of the study. "Losartan's anti-hypertensive properties could mean that patients who have hypertension in addition to cancer may simply have their prescription switched. The hypertension that can result from certain anti-angiogenic therapies may also be managed by losartan, improving the effectiveness of both anticancer therapies " Based on these data, MGH Cancer Center oncologists are planning clinical trials to translate these findings from the laboratory bench to the patient bedside.

Provided by Massachusetts General Hospital