The fight against cancer

Antihypertensive medication halts tumor growth, indicating new drug targets

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Losartan, one of the most commonly used drugs worldwide to control arterial hypertension, halted the growth of skin tumors in murine experiments conducted in the laboratories of the School of Medicine at the University of São Paulo (FMUSP), Brazil. Thus, an old drug has acquired a new application, potentially advancing the quest for new cancer treatments. However, it is too risky to conclude that this drug is ready for human use for this purpose merely because there is a generic, unbranded version available in Brazil and because its side effects are well known.

"Now, we must learn to use this drug to improve tumor treatment," comments physician Roger Chammas, an FMUSP professor and one of the coordinators of this study, which was presented in detail in the May 2010 issue of *Cancer Chemotherapy and Pharmacology*.

Andreia Otake demonstrated that Losartan blocked the action of angiotensin II, a protein fragment (or peptide) that helps control blood pressure, along with other molecules produced by the body. The current study and others studies have shown that angiotensin II may have another, lesser-known and less-explored function:

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helping tumors to form or attract the blood vessels that carry the nutrients required for their survival. With less angiotensin available, fewer blood vessels will develop within the tumor, and tumor death may subsequently occur because of malnutrition. According to Chammas, these studies strengthen the premise that not only the tumor but also the molecules with which the tumor interacts (the tumoral micro-environment) are targeted by the new drugs.

In recent years, several studies have indicated that angiotensin II encourages the migration and proliferation of endothelial cells, which form the innermost layer of blood vessels and, therefore, take part in regulating the inflammatory processes that often underlie the onset or development of tumors. "A tumor can be seen as persistent inflammation, a wound that does not heal and that attracts blood vessels, which, in turn, help to disseminate the cancer throughout the body," comments Chammas. The existence of angiotensin receptors at the surface of endothelial vessels that feed tumors opens up the possibility of new uses for anti-hypertensive medications, such as Losartan. Preliminary trials that are underway (with limited numbers of individuals) in the United States attest to the antitumor effect of this medication, either used alone or in conjunction with antihypertensive drugs that have similar mechanisms of action, such as captopril.

Discovered in 1986 by a group of young researchers at DuPont, losartan was the first in a new class anti-hypertensive drugs called angiotensin II receptor antagonists. Produced by Merck, the drug has been acquiring new applications, although it has become a generic medication in Brazil. One such application is the treatment of chronic kidney diseases. Since the late 1980s, the FMUSP physician Roberto Zatz has conducted studies that show high doses of losartan help to deter the damage caused by chronic kidney disease in rats. Zatz has participated in international clinical studies that have led to the relatively common use today of losartan in the treatment of many kidney diseases. Moreover, it was Zatz who suggested the skin tumor experiment to Chammas; he had hypothesized that tumor growth could be halted by using the ability of this medication to reduce blood pressure, blood vessel growth and inflammatory processes.

At the Federal University of Minas Gerais (UFMG), Robson dos Santos has begun exploring the therapeutic applications of angiotensin 1-7, a derivative of angiotensin II and so named because it has seven amino acids rather than the eight found in angiotensin II. When formulated in cyclodextrin (a sugar) formation, angiotensin 1-7 given orally to rats diminishes the heart cell damage induced by infarction of the heart, as detailed in a study published in the March 2011 issue of *Hypertension*. According to this author, the same formulation can regulate the glucose and lipid (fats) levels, based on laboratory animal experiments. Santos further states that angiotensin 1-7 taken intravenously demonstrated positive effects in the treatment of women with pre-eclampsia, a severe problem that can appear during the second month of pregnancy and is associated with hypertension and liquid retention. According to Santos, trials of this formulation (taken orally) are scheduled to start soon. "We expect to get results within six months," he says. "In pre-eclampsia, exogenous angiotensin 1-7 helps to normalize the level of angiotensin 1-7 in the blood."

Along with these promising results, recommendations on the careful use of anti-hypertensive medication for off-target purposes have emerged. According to a study published in the June 2010 issue of *Lancet Oncology*, individuals who submitted to experimental therapies involving anti-hypertensive drugs acting on angiotensins to treat cardiovascular diseases and diabetes for at least 1 year had a risk that was 1.2 times greater than that of untreated individuals who had developing cancer, particularly lung cancer. Although this risk is small, this finding did attract attention.

In principle, the same drug may combat or spur tumors because cancer is actually a broad set of different diseases; experts have identified some 200 different types of cancer, although all are characterized uncontrolled cell growth that invades neighboring tissues. Increased attention is being given to the unique aspects of each cancer to guide diagnosis and treatment. "Lung cancer in one person can be very different from lung cancer in another person, even if they originated in the same type of lung cell. These differences are evidenced in the different molecular signatures of the tumors and are akin to a fingerprint, as they indicate which molecular pathways have been altered in a given type of cancer," comments Chammas. "We're trying to understand these signatures better in an attempt to improve the diagnosis and treatment of different types of cancer. We must think differently and regard the tumor as an organ that has its own way of working."

The possibility of antihypertensive drugs being evaluated as antitumor medication in Brazil in controlled human trials is remote, given the labyrinth that the researchers and physicians in public institutions face using laboratory data to solve public health problems. The chief complaint is that the approval of a proposed study by the federal bodies can take one year or longer, whereas in the United States or even South Africa, the approval process averages three months. Santos, from UFMG, says that he had to wait for 6 months to obtain all of the approvals required to carry out the angiotensin 1-7 trials with intravenous cyclodextrin to treat women who suffer from severe pre-eclampsia. As

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for the request to test the oral formulation, it took 1 year for the commission of research ethics at the university and from Conep (the National Commission on Research Ethics) at the Ministry of Health to respond. "It's a discouraging reality," he states.

"In Brazil, there is no spirit of urgency," notes Paulo Hoff, the director-general of Icesp (the Cancer Institute of São Paulo), which is tied to the FMUSP medical school and opened in 2008. Icesp currently serves 12,000 new cancer cases every year. "The bureaucracy could be speedier, more efficient and transparent, with no loss of control," says Hoff, one of the authors of an article published in 2010 in *Lancet Oncology*. Hoff proposed joining the governmental, medical and academic interests to plan and execute the initial stages of trials for drugs in countries such as Brazil, primarily to validate the results obtained in countries where the regulation process is speedier. Hoff explains that the interest of the federal government representatives in supporting clinical trials in Brazil seems to be growing. "We must be flexible in our actions," he suggests. "We cannot enter a negotiation imagining that our point of view will be predominant."

Max Mano, an Icesp physician, believes that improved speed in the approval of clinical trials for new drugs or for new applications of older drugs may be particularly beneficial for treating rare tumors, which can appear in any body part and be easily confused with other conditions. In a 2010 article, Mano and Hoff warned that rare tumors account for 25% of all cancer deaths in the United States and possibly in Brazil as well. "A rare tumor is not harder to treat," says Hoff. "What is difficult is finding a doctor who can recognize it and who knows how to treat it."

Certain types of cancer, such as stomach cancer, have become rare in Europe because of the implementation of sanitation measures, improved eating habits and early diagnosis; however, they are still common in Brazil and other Latin American countries. "Many tumors are linked to chronic infectious processes that are not properly addressed," says Mano. "Research is not advancing as fast as the disease." Hoff stresses that there has been progress in standardizing diagnostic tests for different types of cancer, although he acknowledges that "We aren't winning the battle against cancer. We must speed things up." ■

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