Lactic acid found to fuel tumors

November 20 2008

A team of researchers at Duke University Medical Center and the Université catholique de Louvain (UCL) has found that lactic acid is an important energy source for tumor cells. In further experiments, they discovered a new way to destroy the most hard-to-kill, dangerous tumor cells by preventing them from delivering lactic acid.

"We have known for more than 50 years that low-oxygen, or hypoxic, cells cause resistance to radiation therapy," said senior co-author Mark Dewhirst, DVM, Ph.D., professor of radiation oncology and pathology at Duke. "Over the past 10 years, scientists have found that hypoxic cells are also more aggressive and hard to treat with chemotherapy. The work we have done presents an entirely new way for us to go after them."

Many tumors have cells that burn fuel for activities in different ways. Tumor cells near blood vessels have adequate oxygen sources and can either burn glucose like normal cells, or lactic acid (lactate). Tumor cells further from vessels are hypoxic and inefficiently burn a lot of glucose to keep going. In turn, they produce lactate as a waste product.

Tumor cells with good oxygen supply actually prefer to burn lactate, which frees up glucose to be used by the less-oxygenated cells. But when the researchers cut off the cells' ability to use lactate, the hypoxic cells didn't get as much glucose.

For the dangerous hypoxic cells, "it is glucose or death," said Pierre Sonveaux, professor in the UCL Unit of Pharmacology & Therapeutics and lead author of the study, published in the Nov. 20 online edition of

the *Journal of Clinical Investigation*. He formerly worked with Dr. Dewhirst at Duke.

The next challenge was to discover how lactate moved into tumor cells. Because lactate recycling exists in exercising muscle to prevent cramps, the researchers imagined that the same molecular machinery could be used by tumor cells.

"We discovered that a transporter protein of muscle origin, MCT1, was also present in respiring tumor cells," said Dewhirst. The team used chemical inhibitors of MCT1 and cell models in which MCT1 had been deleted to learn its role in delivering lactate.

"We not only proved that MCT1 was important, we formally demonstrated that MCT1 was unique for mediating lactate uptake," said Professor Olivier Feron of the UCL Unit of Pharmacology & Therapeutics.

Blocking MCT1 did not kill the oxygenated cells, but it nudged their metabolism toward inefficiently burning glucose. Because the glucose was used more abundantly by the better-oxygenated cells, they used up most of the glucose before it could reach the hypoxic cells, which starved while waiting in vain for glucose to arrive.

"This finding is really exciting," Dewhirst said. "The idea of starving hypoxic cells to death is completely novel."

Even though hypoxic tumor cells have been identified as a cause of treatment resistance for decades, there has not been a reliable method to kill them. "They are the population of cells that can cause tumor relapse," said Professor Feron.

A significant advantage of the new strategy is that a new drug does not

need to reach hypoxic cells far from blood vessels and it does not need to enter into cells at all – it merely needs to block the transporter molecule that moves the lactose, which is outside of the cells. "This finding will be really important for drug development," said Sonveaux.

The researchers also showed in mice that radiation therapy along with MCT1 inhibition was effective for killing the remaining tumor cells, those nearest the blood vessels. This proved to be a substantial antitumor approach.

Source: Duke University