Keeping at-risk cells from developing cancer

December 10 2007

Researchers at Johns Hopkins have discovered that cancers arising from epigenetic changes - in this case the inappropriate activation of a normally silent gene - develop by becoming addicted to certain growth factors. Reporting online in next week's Early Edition of the *Proceedings of the National Academies of Sciences*, the team shows that blocking this "addiction" can greatly prevent cancer growth.

"If this is translatable to people, it could be really exciting," says Andrew Feinberg, M.D., professor of medicine, oncology and molecular biology and genetics and director of the Epigenetics Center at Hopkins. "It means we might be able to do something about at-risk cells before cancer develops, and treat these cells biochemically and specifically, rather than using current drugs that are nonspecific and kill everything in their path."

The gene for growth factor IGF-II (insulin-like growth factor two) is one of several in the human genome that is controlled by imprinting - where one of the two copies of the gene is turned off, depending on which parent it came from. Normally, the IGF-II gene from your father is turned on and the one from your mother is turned off. Loss of this imprinting causes the activation of the maternal copy, leading to activation of both copies of the IGF-II gene, which has been associated with a fivefold increased frequency of intestinal tumors in people.

The Hopkins team tested mouse cells with imprinting intact, which have only one copy of IGF-II activated, and compared them to cells that had lost imprinting and have both copies of IGF-II activated. They found

that normally imprinted cells respond to normal doses of growth factor and recover within 90 minutes. However, cells that had lost imprinting were activated by the smallest doses and continued to stay activated for more than 120 minutes.

“It’s like they were on a hair trigger, which was totally counterintuitive to what we might have predicted,” says Andre Levchenko, Ph.D., an assistant professor of biomedical engineering at Hopkins and co-director of the study. “You would expect in cells that have lost imprinting, and therefore have twice the amount of gene product, that it would take higher doses to activate the cell. In fact, the cell becomes hypersensitized while having too much IGF-II around.”

The researchers then wondered if blocking the cells’ response to IGF-II could block cancer growth in animals. Mice that develop colon cancer were given a drug that specifically blocks a cell’s ability to respond to IGF-II. These mice developed 70 percent fewer precancerous lesions than mice without treatment.

“Finding the molecular mechanism behind cancer development allowed us to use a specific drug to actually take care of these risky cells before the animal developed cancer,” says Feinberg. “It’s making us think about cancer prevention in a whole new way.”

Source: Johns Hopkins Medical Institutions