Merlin protein found to control liver stem cells, prevent tumor development

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A protein known to be involved in a rare hereditary cancer syndrome may have a role in the regulation of liver stem cells and the development of liver cancer. In the August 15 issue of *Genes & Development*, a Massachusetts General Hospital (MGH) research team describes finding that the protein called merlin, encoded by the NF2 (neurofibromatosis type 2) gene, controls the activity of adult stem cells that give rise to the two major types of liver cells.

"We found that mutation of the NF2 tumor suppressor gene in the mouse liver led to a dramatic overproliferation of liver stem cells - the cells that contribute to the liver's remarkable ability to regenerate," says Andrea McClatchey, PhD, of the MGH Center for Cancer Research, who led the study. "These mice go on to develop the two forms of liver cancer that are most common in humans, suggesting that liver stem cells may be the cells of origin of these tumors."

The liver has a rare ability to regenerate and replace damaged or missing tissue. If one lobe is removed for transplantation, the rest of the donor's organ will return to its previous size and the transplanted lobe will grow to match the needs of the recipient. This regeneration usually involves proliferation of the most characteristic liver cells, called hepatocytes, and of bile duct cells; but if that growth is blocked or those cells are damaged, a population of less-differentiated progenitor cells will start to expand. These liver stem cells have been identified in rodents, and potential equivalents found but not confirmed in humans.

Previous research also indicated that liver stem cells may be the source of some tumors in animals, and suggested that the tumor suppressor gene NF2 may help prevent tumor development. Originally discovered through its involvement in the rare genetic disorder neurofibromatosis type 2, the NF2 gene codes for merlin, a protein known to suppress the activity of a number of cellular receptors. One of these is the epidermal growth factor receptor (EGFR), and oversignaling by that protein is known to lead to several types of cancer. The current study was designed to investigate the role of NF2 and merlin in the fetal and adult mouse liver, including possible involvement with tumor development.

The researchers found that infant mice lacking functioning NF2 in their livers developed dramatic overgrowth of liver stem cells, to the point of crowding out hepatocytes. Mice that did not die from a lack of functioning liver cells soon developed the two major types of liver cancer, and the fact that stem cell overgrowth preceded tumor development strongly suggested that the undifferentiated progenitors were the source of the tumors. Blocking the expression of NF2 in the livers of adult mice had minimal effect on the animals unless a portion of the liver was surgically removed, setting off the regeneration process and leading to the same stem cell overproliferation and tumor development.

McClatchey explains that the study's findings provide new information about liver stem cells and how their proliferation is controlled; identifies a new animal model for liver cancer, the lack of which has seriously impeded understanding the disease; and suggests that liver tumors may originate from liver stem cells and that excess EGFR signaling leads to liver tumor development. "These results are consistent with our previous studies showing that merlin helps to regulate EGFR activity at the cell membrance," she says. "We also showed that merlin's role in cell-to-cell communication is essential for cells to stop growing when they fill the appropriate space. Since liver progenitors need to be poised to

regenerate in case of injury, they may be particularly sensitive to the loss of merlin's regulatory function." McClatchey is an associate professor of Pathology at Harvard Medical School.

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