New genetic marker characterizes aggressiveness of cancer cells

June 26 2007

Levels of a small non-coding RNA molecule called let-7 appear to define different stages of cancer better than some of the "classical" markers for tumor progression, researchers from the University of Chicago report in the June 25, 2007, early online edition of the *Proceedings of the National Academy of Sciences*.

By suppressing genes that are active in the developing embryo, silenced just before birth, and re-activated years later in many advanced cancers, the let-7 family of "microRNAs"—tiny snippets of RNA that can put the brakes on expression of selected genes—appears to prevent human cancer cells from reasserting their prenatal capacity to divide rapidly, travel and spread.

Since they were first discovered in 1993, there had been growing interest in microRNAs and their role in gene regulation. Hundreds of these tiny molecules, about 20 nucleotides in length, have been discovered, scattered throughout the human genome. They act in most cases by attaching themselves to specific sites on messenger RNA, where they block ribosome access and thus prevent production of that protein.

"There may be no human cancer that is not regulated by microRNAs," said study author Marcus Peter, professor in the Ben May Department for Cancer Research at the University of Chicago, "and among microRNAs, let-7 appears to be a key player in preventing a cancer from becoming more aggressive."

"We found that expression levels of let-7 can discriminate more effectively between more and less advanced stages of cancers than any other microRNA," Peter said. "We suspect that loss of members of the let-7 family may be a major determinant of cancer progression."

Understanding how microRNAs such as let-7 keep cancers in check could also point toward a whole new class of anti-cancer therapies, he suggested.

Peter and colleagues focused their initial studies on a standard panel, known as NCI60, of 60 human tumor cell lines that can genetically be divided into two large groups, which they called superclusters 1 and 2. Supercluster 1 cells may represent less differentiated, more aggressive stages of cancer. In contrast, supercluster 2 cells express a gene signature that is consistent with more differentiated, less aggressive cancers.

They tracked down one of let-7's primary targets, a gene called HMGA2, which is overexpressed in a wide variety of cancers. Tumor cells with high levels of let-7, the researchers found, had low levels of HGMA2 and tumor cells with low expression of let-7 expressed high amounts of HMGA2.

Next, they turned to a colleague, gynecologic oncologist Ernst Lengyel, an assistant professor of obstetrics and gynecology at the University of Chicago, whose research group focuses on ovarian cancer. Their theory was first confirmed with ovarian cancer cell lines and then the Peter/Lengyel team tested HGMA2 protein levels in tumor samples from 100 patients with ovarian cancer.

Neither normal ovarian tissue nor benign ovarian tumors expressed HGMA2, they found. However full blown carcinoma expresses large quantities of HMGA2. They also found that a high level of HGMA2 was highly correlated with poor prognosis, and that high HGMA2 levels were

closely tied to low let-7 expression.

By combining the two measures, high HGMA2 and low let-7, they could separate the patients into two groups, and predict outcome. Five-year progression-free survival for patients with high let-7 and low HGMA2 was nearly 40 percent. For patients with low let-7 and high HGMA2, it fell to less than 10 percent.

"Our data suggests that human tumors can be divided into two major subtypes, the let-7hi and let-7lo-expressing tumor cells," the authors write. This separation may not be restricted to ovarian cancer, or to the NCI60 panel of tumor cells, they suggest, but could apply to a multitude of tumor types.

"There is growing evidence that large-scale gene-expression patterns can be regulated by microRNAs", Peter said. "Many of them are beginning to be expressed shortly before birth, where they turn off genes that were necessary for the rapidly developing embryo. Probably a number of embryonic genes, after being turned off for decades, are reexpressed in cancer cells, enabling those cells to regain their embryonic capacity to move around and invade other tissues."

The loss of let-7, the authors argue, could be seen as one crucial step in this process of tumor progression. One of its functions, they argue, is to maintain differentiated states by preventing the expression of embryonic genes such as HMGA2.

No rapid test of let-7 level is available for clinical use. "The levels are difficult to quantify in clinical samples", Peter said but "technology is exploding right now. We may be able to do this clinically before too long."

Source: University of Chicago