MedicalXpress

Researchers find roadmap to next-generation cancer therapies

May 25 2008

Pinpointing new targets for cancer treatments is as difficult as finding a needle in a haystack, yet a University of Rochester team has discovered an entire novel class of genes they believe will lead to a greater understanding of cancer cell function and the next generation of effective and less harmful therapies for patients.

In a paper in the journal *Nature*, available online May 25, the researchers describe how multiple cancer genes cooperate to cause malignant cell transformation. Further, they describe the discovery of approximately 100 genes that work downstream of known cancer-causing mutations, providing a host of new opportunities for intervention.

“We believe that we have found a cornerstone for development of new treatments that ultimately will allow selection of drugs and drug combinations from a pool of compounds directed against these new genes,” said lead author Hartmut Land, Ph.D., professor and chair of the Department of Biomedical Genetics at the University of Rochester Medical Center and scientific director of the James P. Wilmot Cancer Center at the URMC.

“However, much more work needs to be done to explore how our findings may lead to successful targeting of various cancer types and cancer stem cells,” he said.

Targeted cancer therapy – such as the drug Gleevec that works for patients with certain types of leukemia and gastrointestinal tumors – is

based on a keen understanding of the architecture of cancer. Much has been learned in the past several years, but what has been lacking is a clear roadmap leading to dozens of new molecular targets.

Twenty-five years ago Land was among the first scientists to discover that malignant cell transformation required multiple mutations in distinct cancer genes. Ever since, he has been studying the cooperative nature of this process and the inner workings of cancer cell function.

His research group began testing, at the genomic scale, a prediction that genes responding synergistically to cooperating oncogenic mutations might act as the “drivers” toward malignancy, Land said. It now appears that this hunch has paid off.

Spear-headed by co-authors Helene R. McMurray, Ph.D., a post-doctoral fellow, and graduate students Erik R. Sampson, George Compitello and Conan Kinsey, the team found that among 30,000 cellular genes, only about 100 genes responded synergistically to the combination of two of the most prevalent cancer genes, Ras and p53, and were expressed differently in normal and cancer cells.

Accordingly, the research group termed these 100 genes CRGs, for “cooperation response genes.” By studying a subset of the CRGs, researchers also found that 14 of 24 CRGs were essential to tumor formation. In contrast, only one of 14 genes responding in a non-synergistic manner (non-CRGs) had a similar effect.

The significance of Ras and p53, and by association the CRGs, is enormous. Ras and p53 are implicated in about half of all cancers. When p53, a tumor-suppressor gene, loses its function, and when Ras becomes hyperactive, both genes play major roles in promoting uncontrolled growth of colon, pancreas and lung cancers.

Ras activation and p53 loss-of-function cooperatively work together through the CRGs, which encode proteins that regulate cell signaling, cell metabolism, self-renewal, cell differentiation and cell death.

“Indeed, CRGs may provide us with a surprisingly large and valuable set of targets for interventions that will destroy cancer cells and leave normal cells unharmed,” Land said. “We are very excited with the results.”

Source: University of Rochester