Telomere failure, telomerase activation drive prostate cancer progression

February 21 2012

Genomic instability caused by an erosion of the protective caps on chromosomes, followed by activation of an enzyme that reinforces those caps, allows malignant cells to evade destruction and acquire more deadly characteristics, researchers report in an Online Now article at the journal *Cell*.

In a strain of mice engineered to develop prostate cancer, all mice that went through this two-step process developed lethal cancer and 25 percent had the disease spread to the spine. Two groups of mice that avoided this cycle developed only precancerous lesions or localized prostate cancer.

A comparative analysis of genetic changes in the metastatic mouse tumors and those found in metastatic human prostate cancer identified the Smad4 gene as a driver in bone metastasis. Fourteen other genes were found to be associated with human prostate cancer prognosis.

The research focused on telomeres - repeat nucleotide sequences at the tips of chromosomes that prevent genomic damage during cell division. Telomeres shorten with each cell division, eventually permitting genomic instability in the cells that normally causes these abnormal cells to die.

In cancer the enzyme telomerase becomes activated and lengthens telomeres, preserving damaged cells to survive and reproduce. Telomerase is inactive in normal cells.

Telomerase activation confers new strengths on tumors

"These in vivo mouse studies, together with human and mouse prostate cancer genomic data, provide evidence that telomere dysfunction plays a critical role in prostate cancer initiation and progression," said co-senior author Lynda Chin, M.D., professor and chair of The University of Texas MD Anderson Cancer Center's Department of Genomic Medicine.

"Our studies also show that telomerase activation after genomic instability caused by telomere dysfunction enables evolving cancers to progress and acquire new biological properties, including central features of advanced human prostate cancer," Chin said.

Chin, co-senior author and MD Anderson President Ronald DePinho, M.D., and colleagues conducted this research while at Dana-Farber Cancer Institute in Boston.

Telomere dysfunction, fired-up telomerase, cause bone metastasis

The team took a strain of mice with both the p53 and pten tumor-suppressing genes knocked out that normally develop nonmetastatic prostate cancer and engineered some to express telomerase. They were cross-bred for several generations.

- Control mice with intact telomeres (either wild-type mice or those with telomerase expressed) avoided the genomic instability caused by telomere shortening. All of these mice developed locally invasive, nonmetastatic prostate cancer.

- Mice without telomerase were subject to telomere dysfunction and genetic changes and developed precancerous high-grade prostate intraepithelial neoplasia (HPIN) but 60 percent of them did not progress to prostate cancer. Signs of programmed cell death triggered by genetic abnormalities abounded in this group.
- Mice subject to telomere dysfunction, genomic instability and telomerase activation also developed HPIN but then progressed to lethal bulky tumors, with 5 of 20 developing spinal metastases that were not seen in the genome-stable mice.

"Not only did telomerase reactivation bypass the cancer progression block that arises with telomere dysfunction, it also conferred a new property - bone metastasis - that was not seen in tumors that did not go through telomere dysfunction followed by telomerase reactivation," said first author Zhihu Ding, Ph.D., formerly of Dana-Farber and now with Sanofi-Aventis, Inc.

"This provides the first genetic evidence that telomerase reactivation and genome stabilization are necessary to drive full malignant progression in epithelial cancers," Ding said.

Aligning genetic alterations in mice and humans

Chin, Ding and colleagues analyzed gene copy number aberrations - genes deleted or amplified - in 18 advanced tumors from the mice and 194 human prostate tumors.

They found 22 of the 94 copy number alterations involving deletion or amplification of 741 genes identified in mice were similar to those found in humans. A series of analyses of changes found in bone metastases pointed to deletions of the Smad4 tumor-suppressor gene, which regulates the transforming growth factor beta (TGF-ß) pathway.

The team took this finding back to the mouse model with tumor suppressors p53 and pten knocked out. These mice don't develop bone metastasis, but when the researchers also knocked out Smad4, more aggressive tumors developed, including bone metastasis in three of 24 mice.

Genes prognostic for human prostate cancer

Next, they looked at 14 genes in nine molecular pathways found to be enriched in bone metastasis to see if they were prognostic for recurrence (as measured by PSA levels after surgery) among 140 prostate cancer patients.

The 14-gene set was significantly prognostic of biochemical recurrence, providing evidence of their biological relevance to human prostate cancer, but the researchers noted that their individual contributions and mechanisms of action will require further research.

"Overall, our findings validate the integrative approach of employing genotype-phenotype correlations found in the mouse model with the power of genomic and bioinformatic analyses to discover and explain molecular mechanisms that drive prostate cancer," said co-first author Chang-Jiun Wu, Ph.D., a postdoctoral fellow in MD Anderson's Department of Genomic Medicine.

Provided by University of Texas M. D. Anderson Cancer Center