Genetic Changes in Stroma Linked to Head-and-Neck Cancer

Judith Groch

Reviewed by Zalman S. Agus, MD; Emeritus Professor at the University of Pennsylvania School of Medicine.

Be aware that the finding of genetic changes in the tissues of patients with smoking-related head-and-neck cancer came from a preliminary study and await further identification of biomarkers for targeted therapy and prevention.

CLEVELAND, Jan. 9 -- In smoking-related head-and-neck squamous-cell carcinoma, genetic alterations in the apparently non-malignant connective tissue and in the epithelium have been found, according to a preliminary study.

A correlation between tumor aggressiveness was found for three stroma-specific and two epithelial-specific "hot spots," reported Charis Eng, M.D., Ph.D., of the Cleveland Clinic, and colleagues, in the Jan. 10 issue of the Journal of the American Medical Association.

Carcinogens associated with head-and-neck squamous-cell carcinoma can inflict genomic alterations not only on the epithelium but also on the mesenchyme of the aerodigestive tract, they wrote. Therefore, the apparently nonmalignant connective tissue surrounding the tumor epithelium can acquire genomic alterations and contribute to cancer initiation and progression.

"Our data suggest that this genetically altered mesenchymal field might provide the soil that facilitates the squamous-cell carcinoma head and neck invasion and metastases," they added.
Genetic Changes in Stroma Linked to Head-and-Neck Cancer

Judith Groch
Reviewed by Zalman S. Agus, MD, Emeritus Professor at the University of Pennsylvania School of Medicine.

It is an accepted concept that the cancer arises from a successive accumulation of genetic alterations in the squamous epithelium of the mucosa that will allow a cell to obtain a growth advantage, escape apoptotic signaling, clonally expand, and ultimately invade and metastasize, the researchers wrote.

To track these changes, tumor epithelium and also surrounding stroma were isolated from 122 U.S. patients with oral cavity and oropharyngeal or hypopharyngeal squamous cell carcinoma. The tissues were given whole-genome LOH/AI (loss of heterozygosity or allelic imbalance) analysis, using 366 microsatellite markers. Overall, 244 samples from these patients included 122 epithelium and 122 stroma samples.

Samples, collected between 2001 and 2004, were pulled and transferred in batches of 10 to 30 between 2002 and 2005. Laser capture microdissection DNA extraction and technical genotyping occurred on a rolling model from 2002 to 2005.

Tumor-associated stroma of head-and-neck squamous cell carcinoma from smokers were found to have a high degree of genomic alterations, the researchers reported.
Genetic Changes in Stroma Linked to Head-and-Neck Cancer

Judith Groch
Reviewed by Zalman S. Agus, MD; Emeritus Professor at the University of Pennsylvania School of Medicine.

A correlation between tumor aggressiveness was found for a specific set of five loci. Three stroma-specific loci (D4S2417, D3S360, and D19555) were associated with tumor size and regional nodal metastases, the researchers reported.

Furthermore, they said, two epithelial-specific LOH/A1 hot spots were positively correlated with regional nodal metastases and clinical stage. A hot spot was defined as a locus having a significantly high frequency of LOH/A1 compared with all other loci on the same chromosome.

There was no difference in the number of informative markers between the stroma and epithelium (48.4% versus 48.9%). For the epithelium, the detection frequency per sample was 69.0% (range, 33.3%-93.7%) compared with 64.4% (range, 25.8%-90.3%) observed in the stroma (P=.10).

Interestingly, the researchers said, there were more hot spots in the stroma than in the epithelium. This may indicate that only a limited set of key genetic alterations within the epithelium are required to initiate head-and-neck cancer genesis, while other alterations are downstream or even bystander events. Whether the accumulation of stromal alterations occurs concordant with the neoplastic transformation of the epithelium or, in fact, precedes it is unknown, they wrote.
Genetic Changes in Stroma Linked to Head-and-Neck Cancer

Judith Groch
Reviewed by Zalman S. Agus, MD; Emeritus Professor at the University of Pennsylvania School of Medicine.

These observations, they said, suggest that these genes in concert may play a role in head-and-neck squamous-cell carcinoma and are particularly relevant to regional metastases. "It is tantalizing that the most promising candidate genes in the regions of loss associated with clinicopathologic features belong to the various repair pathways."

The loss, for example, of FANCD2, FAZF, and ERCC2 together could additively and more severely result in additive loss of repair capabilities that result in a cascade of downstream genomic alterations, leading to genomic instability resulting in invasion and metastasis.

These observations suggest that the apparently nonmalignant stroma of this cancer is rich in genomic alterations. The data suggest that this genetically altered mesenchymal field might provide the soil that facilitates carcinoma invasion and metastases, the researchers said.

"We hope that our genomic observations, which point to genomic regions that may harbor many genes, will guide future in-depth functional and mechanistic studies," Dr. Eng concluded. "Nevertheless, our current observations can be used to identify new biomarkers for prediction of clinical outcome and potentially novel compartments for targeted therapy and prevention."

Pages: 1 2 3 4 5