

Perspective

Perspective on Zhang et al., p. 1081

Genetic Driver Events in Premalignancy: LOH Validated for Marking the Risk of Oral Cancer

Webster K. Cavenee

Abstract

In this issue of the journal (beginning on page 1081), Zhang and colleagues extend the 30-year-old discovery of LOH profiles to provide validated markers of oral premalignant lesion risk for cancer. They prospectively show a dramatic difference in cancer progression between high-risk lesions (LOH) and low-risk (non-LOH) lesions ($P = 0.002$). This work has important implications for oral cancer prevention and risk modeling and for understanding genetic driver events in premalignancy. *Cancer Prev Res*; 5(9); 1073–4. ©2012 AACR.

It has been nearly 30 years since we (1) described chromosomal mechanisms that unmasked the inactivating, recessive mutations in human cancer that had been theoretically predicted a decade before based on statistical considerations (2). We termed the group of these mechanisms as "LOH" as the data showed that certain specific regions of a patient's normal genome that were biallelic could become monoallelic in their tumors. This, together with the familial segregation of autosomal dominant cancer occurrence, suggested that a loss-of-function mutation was being transmitted that was uncovered by the chromosomal losses in particular cancer progenitor cells. In fact, the use of such LOH allowed direct genetic proof that such tumor suppressor gene mutations could cause predisposition to neoplastic disease (3), that such genes could have pleiotropic effects in humans so that their identification was important for the etiology of more than one cancer (4, 5), and that LOH could be used to provide the first accurate premorbid predictions of cancer development in humans (6).

Since then, LOH has been shown to unmask not only mutated inactive alleles but also epigenetically fully/partially inactivated ones and thereby to provide a continuum of tumor suppressive functions (7). In all of these guises, LOH has been shown, by many groups throughout the world represented in more than 25,000 publications from a recent PubMed search, to be involved in most forms of human cancer development and progression and to pinpoint the chromosomal location and genetic activity of almost all familial predispositions to cancer development. The net effect of these chromosomal alterations is the downregulation of tumor suppressor activity and resultant

release of growth constraints as first shown in retinoblastoma (8).

The use of LOH as markers of the risk of cancer progression cancer risk has had less emphasis. However, there is no reason, in principle, that the cancer-specific LOH that occurs in early stages of tumor progression [and that require additional genetic hits of various types (9–11) for ongoing progression] should not provide robust markers for these predictive purposes.

In this issue of the journal, Zhang and colleagues (12) report an incisive test of the suitability of LOH in premalignant lesions for such predictive use. They tackle one of the vexing problems in cancer care: how can premalignant lesions be parsed into groups with a high propensity to progress to malignancy from those that do not? Although this is an issue for many forms of epithelial cancer, the authors focus on oral squamous cell cancer. In this disease, the occurrence of oral premalignant lesions (OPL) is common and predicting which bears a high risk for malignant progression could be of significant value in following those patients with OPL so as to have the earliest possible intervention, saving those patients with low-risk OPL from frequent screening and, perhaps, as early markers of therapeutic response.

Early studies of OPL (13) had indicated that LOH for chromosomes 9p and 3p were common, and this team's initial retrospective analyses of 116 patients with known cancer outcomes (14) had shown a large (~20-fold) increase in risk of disease progression for patients with OPL demonstrating LOH for the short arms of chromosomes 3 and/or 9. In the present work, they test this in a large (296 patients) prospective cohort through the auspices of the community-based Oral Cancer Prediction Longitudinal Study that follows oral cancer patients with mild or moderate dysplastic lesions. When such lesions were microdissected and subjected to LOH analysis using microsatellite markers for chromosomes 3p and 9p, those lesions could be separated into groups with allele retention or those with LOH. In the former group, only 1 of 100 progressed, whereas the latter pattern was detected in nearly all

Author's Affiliation: Ludwig Institute for Cancer Research, University of California, San Diego, La Jolla, California

Corresponding Author: Webster K. Cavenee, Ludwig Institute for Cancer Research, University of California, San Diego, La Jolla, CA. E-mail: wcavenee@ucsd.edu

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progressing lesions (different with a *P* value of 0.002). Although these results were similar to the initial retrospective analysis (14), the authors took steps to further extend and refine the model using data from other chromosomal regions. This led to 3 categories of risk for progression with high statistical significance: low risk that retained heterozygosity for chromosome 9p; intermediate risk that had LOH for 9p alone or LOH 9p plus either LOH for 17p or LOH for 4q; or high risk that showed LOH for 9p, 17p, and 4q. The data were then validated in the original retrospective cohort and when the 2 cohorts were combined. It is important to note that these LOH events may be the cause of functional inactivation of known target genes, thereby sufficing as strong driver events (i.e., *CDKN2A* on chromosome 9p, *TP53* on 17p), whereas the less predictive values of others (i.e., LOH for chromosome 4q and, especially, 3p) might reflect, at least in oral premalignancy, the genetic distance of the LOH markers from a bona fide suppressor gene, passenger events, or weaker epistatic interactions with the stronger drivers.

Interestingly, although oral cancer and leukoplakia occur largely in smokers, when leukoplakia occurs in a nonsmoker, it presages a high risk for progression (15). Covariate and multivariate analyses of the LOH and clinical data from the present studies support this. The mechanistic explanation for this is unknown at present but indicates an area for further research. Finally, the use of these LOH markers for stratifying patients for treatment with EGF receptor (EGFR)

inhibitors is under way in Phase II trials and for defining eligibility (based on high risk) for EGFR inhibitor treatment in the personalized Phase III Erlotinib Prevention of Oral Cancer (EPOC) trial. EPOC has pioneered the prospective use of real-time LOH profiling in a clinical trial setting (<http://clinicaltrials.gov/ct2/show/NCT00402779?term=oral+cancer+prevention&rank=1>).

In sum, these extraordinarily well-done and well-analyzed studies underscore the use of LOH in community-based risk assessment and, perhaps, in patient therapeutic and prevention stratification schemes. As such, this represents a major advance for a decades old idea that has been waiting for such a test. It also underscores the value to patients of funding mechanisms [such as the National Cancer Institute Specialized Programs of Research Excellence (SPOR) grant under which the present studies were performed], as well as those that enable the collection and continuous characterization of uniquely valuable patient populations, such as the Oral Cancer Prediction Longitudinal Study that was employed to such benefit here. Lastly, this work has important implications for cancer prevention and risk modeling in premalignant lesions of the oral cavity and other sites.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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