Most of the cancers that arise in the mucosa of the upper aerodigestive tract, including the oral cavity, pharynx, and larynx, are squamous cell carcinomas. To date, although there are no primary mutations that have been discovered to cause these cancers, aberrant expression of a variety of molecules characterizes head and neck squamous cell carcinoma (HNSCC). Most of the studies have compared expression levels in primary HNSCCs with levels in corresponding normal mucosa (generally harvested from the surgical resection margins). The advantage of such an approach is that both normal and tumor tissue are derived from the same patient and, hence, have been exposed to the same environmental risk factors (i.e., tobacco and alcohol exposure). In addition, because patients who are cured of their primary HNSCC have a lifelong risk of second primary tumor formation, genetic and epigenetic alterations that occur in the “condemned mucosa” may reflect early carcinogenic changes. Conversely, if an alteration is isolated to the tumor tissue and is not detected in the adjacent normal tissue, it may represent a relatively late event.

To determine the biological and clinical significance of the elevated mRNA or protein that is detected in tumor tissue, expression levels can be examined in association with factors that are known to contribute to clinical outcome as well as survival itself. For HNSCC, the clinical and pathologic features that influence patient outcome include the size of the tumor (T stage), the presence and extent of cervical nodal metastases (N stage), and the presence of distant metastasis (M stage). The power of such an approach is strengthened if the patient population is relatively homogeneous with respect to tumor and treatment characteristics and depends on close and regimented clinical follow-up. However, if associations are discovered, it is often difficult to discern the mechanism(s) of how the elevated mRNA or protein contributes to survival.

In the study by Reiter et al. (1) in this issue of Clinical Cancer Research, tumor and adjacent normal mucosa from 66 HNSCC patients were analyzed for expression of Aurora kinase A (AURKA/STK15/BTAK). The rationale for examining this kinase in HNSCC is based on studies in other epithelial malignancies showing that up-regulation of AURKA induces chromosomal instability leading to aneuploidy and transformation. In this population, AURKA was measured in primary tumors and marginal mucosa by both real-time quantitative reverse transcription-PCR and immunohistochemistry using a tissue microarray fashioned from a subset of the 66 cases (34 of 66). The strength of using both approaches includes the opportunity to examine the correlation between mRNA and protein expression levels (here, they were consistent). In addition, in the absence of extracting RNA from microdissected samples, it is not possible to determine the specific contribution of tumor cells to the mRNA species being measured. Combining immunohistochemistry with quantitative reverse transcription-PCR allows for subcellular localization as well as quantitative expression level determinations.

AURKA is a member of the Aurora/lpI1p family of cell cycle–regulating serine/threonine kinases. The gene for AURKA maps to 20q13.2 and is localized at interphase and mitotic centrosomes and at the spindle poles where it regulates proper chromosome segregation and kinesis (2). Centrosome abnormalities in these tissues were analyzed using indirect immunofluorescence. Centrosomes were considered abnormal when they were at least twice the size of those seen in control cells (the nonneoplastic epithelium). Fluorescence in situ hybridization was used to evaluate chromosomal aneusomy (chromosomes 9, 15, and 20). Aneusomy was defined by the presence of at least 25% of the nuclei having several centromeric signals for at least one chromosome different from two signals corresponding to disomy.

The population consisted of 66 patients with primary HNSCC tumors derived from a variety of sites in the upper aerodigestive tract. Although all patients underwent surgery to obtain tissue, it is not clear if the procedures consisted of biopsies or resections with curative intent (or both). In fact, the approach to treatment for the cohort (radiation, chemotherapy, etc.) is not discussed. AURKA mRNA expression showed up-regulation in the tumor (compared with the normal) where levels correlated strongly with tumor and nodal classification as well as distant metastasis. Immunohistochemistry on the subset of tumors showed that AURKA protein was primarily localized to the cytoplasm. Using a semiquantitative technique where >30% of cells staining was considered strongly positive (3+) and <10% of cells staining was considered weakly positive (and no staining was negative), protein levels correlated with regional lymph node and distant metastasis. Of the only 29 tumors analyzed, 18 were found to have centrosome abnormalities, and all of the 32 tumors studied showed chromosomal aneusomy. Because all of the tumors showed aneusomy, it is not possible to assess the association of this variable with other features. Curiously, the investigators found that AURKA mRNA, but not protein, expression levels correlated with disease-free survival and overall survival. This discrepancy may be due to post-translational modifications of AURKA mRNA or, more likely, the limited quantitative information provided by the immunohistochemistry of the tissue microarray. Because
AURKA levels correlated with N stage, which to date has been the most important predictor of survival in HNSCC, it would be worthwhile to determine if the contribution of AURKA levels to survival is independent of nodal metastases.

Prior studies have reported DNA gains on chromosome 20q in HNSCC (3). AURKA maps close to the critical region of this DNA gain; therefore gene amplification could contribute to overexpression of this molecule in HNSCC. Further mechanistic studies using HNSCC tumors and cell lines will elucidate the mechanisms of AURKA up-regulation in this tumor system. The functions of AURKA in HNSCC remain unknown. In other tumor systems, AURKA has been shown to mediate cell migration and tumor cell invasion (4) as well as cell growth and tumorigenicity (5). The report by Reiter et al. in this issue of Clinical Cancer Research is the first report of AURKA in HNSCC. The findings of increased expression and the association of AURKA elevation with decreased survival suggests that further studies to determine both the mechanism of increased expression as well as the functional consequences of elevated AURKA in this tumor system are warranted.

References

Prognostic Biomarkers in Head and Neck Cancer

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