Squamous cell cancer

Daniel L Van Dyke

Department of Medical Genetics, Henry Ford Health System, 2799 West Grand Boulevard, Clara Ford Pavillion, Detroit, MI 48202, USA (DLV)

Published in Atlas Database: September 2001
Online updated version : http://AtlasGeneticsOncology.org/Tumors/SquamousCellID5130.html
DOI: 10.4267/2042/37819

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2002 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Clinics and pathology

Disease

Squamous cell carcinoma (SCC) accounts for the majority of non-small cell lung cancer, other bronchial tree cancers, and cancers arising throughout the upper aerodigestive tract including the oral cavity, paranasal sinuses, pharynx, larynx, trachea, and esophagus. SCC is the second most common skin cancer. SCC arises at many other sites such as salivary gland, esophagus, bladder, penis, and the female genital tract.

Etiology

Environmental exposures such as tobacco, alcohol, chronic mucosal irritation, certain human papilloma viruses, actinic or low dose radiation, and some occupational chemical exposures increase the risk of developing SCC. The DNA of HPV 16, 18, and 31 have been found in human genital cancers and HPV 16 and 18 have been recognized in verrucous carcinomas of the larynx and SCC of the tongue and tonsil. Epstein Barr virus (EBV) is a risk factor for nasopharyngeal SCC in southern China and the Aleutians. Sunlight exposure is the major causal factor in SCC of the skin. In the East and Far East, oral cavity and oropharyngeal cancers account for almost one-half of all cancers. In Bombay, 50% of all cancers are in the buccal mucosa, and is associated with chewing pan.
Specific TP53 mutations are associated with tobacco exposure. Deletions and allelic losses of 9p are more common in smoking-associated SCC.

Epidemiology

There is strong evidence that SCC has a genetic basis. For families with smoking-related malignancies, genetic segregation analysis showed strong evidence favoring an autosomal dominant pattern of inheritance for predisposition to malignancy. Some individuals with SCC appear to have a heritable sensitivity to chromosome breakage by certain clastogens.
Of mendelian diseases, xeroderma pigmentosum and Bloom syndrome carry a significant risk of skin SCC. Nasopharyngeal carcinomas are 25 times more frequent in Kwang Tung Province, China than in whites with certain HLA haplotypes and familial clustering being identified. Chinese who emigrated from Kwang Tung retain a significantly higher risk of developing nasopharyngeal carcinoma.

Pathology

Histologic grading (tumor, node, metastasis, TNM) and evaluation of tumor thickness have been used to predict survival and to develop algorithms for further treatment.
The tissues surrounding an SCC often exhibit genetic damage and premalignant lesions, perhaps secondary to the same carcinogens, and this entire "cancerization field" appears to be at risk for second primary cancers.
DNA content and ploidy are correlated with tumor aggressiveness and responsiveness to some treatments. Abnormal DNA content has been thought to reflect altered proliferation capacity of tumor cells and has been associated with adverse biologic and clinical behavior. Although most studies suggest worse prognosis and more aggressive behavior in aneuploid tumors, these findings are not universal. At some anatomic sites, aneuploid tumors have a better prognosis, and improved response with advanced differentiation.

Treatment

Treatments have resulted in modest improvements in survival in recent years. For head and neck SCC, standardized with traditional therapies relying on surgery, radiation therapy, or combined surgery-radiation therapy treatments. Recent efforts in new
treatment strategies have revolved around adjuvant or concomitant chemotherapy. For most skin SCC, surgical excision is standard practice.

**Prognosis**

Largely depends on pathological stage at diagnosis, which in turn depends to a great extent on the anatomic site. For example, skin SCC and larynx SCC have a relatively favorable prognosis because they are frequently identified at an early stage. SCC of the nasopharyngeal area is less often detected early, and the rich blood supply and lymphatic anatomy of the nasopharynx encourages early metastatic disease and a generally less favorable prognosis.

**Cytogenetics**

Note

The karyotype is typically very complex, but common features in SCC at one anatomic site are often very similar to SCC at other anatomic sites, irrespective of the initiating events (tobacco and alcohol, pan, human papilloma virus, etc.). These common changes strongly suggest that initiation, development, and progression of squamous epithelial neoplasia are controlled by some of the same genetic pathways, irrespective of anatomic site.

**Cytogenetics Morphological**

Most early cytogenetic studies of SCCHN relied on analysis of later stage tumors and established cell lines. More recent studies included short term cell cultures, and by-and-large the results have been similar. A common sequence of SCC karyotype evolution appears to be initial loss of chromosomes or segments, followed by tetraploidy and ultimately loss of previously uninvolved chromosomes from the tetraploid population. The hypotetraploid cell population can have a near triploid or even lower DNA index and number of chromosomes. Many tumors exhibit both diploid and tetraploid cell subclones. As with high DNA content, polyploidy is associated with a more aggressive growth pattern in vitro, high histopathologic grade, and poor survival. Earlier stage tumors tend to have more simple karyotypes. However, within every pathological stage some tumors have more complex karyotypes. It has been difficult to assemble a “typical” cascade of genetic evolution that has broad applicability in SCC, because most of the recurrent abnormalities have been observed at every histopathologic stage. Nevertheless, some recurrent cytogenetic changes tend to arise earlier in tumor development, and others tend to confer greater prognostic importance. Common early changes in head and neck SCC include 9p and 3p deletion, and 17p mutation, with 5q, 8p, 18q, 21q loss and 11q gain arising later and involved in disease progression. Few specific rearrangements or breakpoints have been documented, and most of those are typically associated with the recurrent gains and losses of chromosome segments. Unbalanced translocations involving bands 1p11-p12, 5q13, 10p11.2, 18q11.2, 11q13, and 7q11.2 were typically associated with deletions. Likewise, isochromosomes 3q, 5p, 7p, 8q, and 9p are typically associated with duplication of the arm involved in the isochromosome, and deletion of the other arm 81. Deletions involving 3p suggest at least three distinct targets of loss. The most universal class of cytogenetic change is deletion, also observed as loss of heterozygosity (LOH) in molecular genetic studies. Loss of segments of 3p, 5q, 8p, 9p, 10p, and 18q are among the most common. The most frequent loss involved 3p. SCC exhibit recurrent gain of segments within 3q, 5p, 7p, 8q, distal 1q, and 11q13-q23. Duplication 11q13-q23 and an apparent homogeneously staining region (hsr) at 11q13 or 11q21 is relatively common. An hsr with amplification of PRAD1/CCND1 can be located in 11q or elsewhere.

**Cytogenetics Molecular**

FISH analysis of SCC in vivo (from histologic sections) has helped show that the karyotypes observed in established cell lines accurate reflects that of the tumor. FISH has also shown that many apparently independent primary tumors are monoclonal. Comparative genomic hybridization (CGH) studies have generally paralleled classical cytogenetics, although several important differences in findings between the two techniques remain an area of interest.

**Genes involved and proteins**

Note

Studies at the molecular level have helped to clarify some of the cytogenetic observations of recurrent gain and loss of specific segments. Allelotype studies, and similar cytogenetic studies, have described a poorer prognosis as genetic losses accumulate. As with cytogenetic studies, allelotype results are fairly similar across anatomic sites, and are even similar to those of adenocarcinomas of the lung. Some genetic abnormalities have been recognized by microsatellite studies that were not common changes in classical cytogenetic studies (e.g., 4q and 15q deletions and 3q amplification). Mismatch repair gene mutations play a negligible role in the etiology and evolution of SCC. Microsatellite instability has been reported, but does not appear to be a major factor in most SCC.

**Location: Chromosome arm 3p**

Somatic mutations: The most frequent autosomal abnormality is loss of 3p (50-75% of tumors). It appears very early, e.g. in bronchial and esophageal epithelial dysplasias. Isochromosome 3q usually associated with loss of 3p. Other deletions reveal three independent regions of loss at 3p14 (FHIT/FRA3B),
3p21, and 3p24-p45. Specific targets at 3p21 remain elusive but DCL1 is a candidate. The VHL (von Hippel Lindau) locus may be the target of 3p24-p25 deletion.

**Location: Chromosome arm 3q**
Somatic mutations: Duplication 3q is often associated with isochromosome formation and there is almost always 3p loss in the same tumor. CGH studies suggest one or more regions of amplification within 3q, and p63, a p53 homolog, is a possible target of gain at 3q27-3q29.

**Location: Chromosome arm 5q**
Somatic mutations: Frequent gains of 7p may permit increased activity of EGFR, which is amplified in some SCC. Amplification is associated with lymph node involvement in esophageal SCC.

**Location: Chromosome arm 8p**
Somatic mutations: Distal 8p loss is a recurrent abnormality, and may target different genes in 8p21, 8p22-p23, and 8p23. FEZ1, a transcription factor residing at 8p22, may be one genetic target for deletion. In lung SCC, 8p deletion is an intermediate event, following after 3p and 9p deletion.

**Location: Chromosome arm 9p**
Somatic mutations: Loss of 9p is a common and usually early event. The tumor suppressor gene p16/CDKN2/MTS1 at 9p22 is the most likely primary target of deletions. Homozygous deletions and promoter methylation have been identified. In cervical SCC, 9p deletion is associated with lymph node metastasis.

**Location: Chromosome arm 10p**
Somatic mutations: Loss of 10p has been observed in many SCC.

**Location: Chromosome arm 11q**
Somatic mutations: The region 11q13-23, commonly duplicated or amplified, includes several probable target genes: HST1, INT2, PRAD1/CCND1, and EMS1. PRAD1/CCND1 and EMS1 are often amplified and over expressed. PRAD1/CCND1 over-expression may be associated with radiosensitivity. An 11q duplication is associated with lower survival in esophageal SCC and disease progression in SCCHN.

**Location: Chromosome arm 13q**
Somatic mutations: Loss is associated with lymph node metastasis in esophageal SCC. RB1 or BRCA2 may or may not be the target.

**Location: Chromosome arm 16q**
Somatic mutations: 16q deletion is a less common but recurrent finding in SCC at several anatomic sites. E-cadherin is one candidate target.

**Location: Chromosome arm 17p**
Somatic mutations: TP53 gene mutations are initiating or very early events in SCC regardless of anatomic site, already evident in premalignant lesions and are not usually correlated with tumor aggressiveness or survival. Deletion of 17p is very common and may frequently serve to inactivate the remaining normal homolog in a tumor with a TP53 mutation. In cervical SCC, 17p loss appears to be a late event correlated tumor invasion. The specific mutations are directed by the mutagen involved, e.g., smoking and alcohol in larynx, betel nut in buccal mucosa, and human papilloma virus in vulvar SCC.

**Location: Chromosome arm 18q**
Somatic mutations: Loss of 18q, specifically 18q21-q22, is a very poor prognostic indicator in SCC at many sites, including the head and neck and the female genital tract. The primary target of loss in SCC is unknown, but probably exclude Smad2, Smad4, and DCC.

**Location: Chromosome arm 21q**
Somatic mutations: Monosomy 21 is common. Uncommon 21q deletions point to a ubiquitin-specific protease gene as the possible target.

**Location X and Y chromosomes**
Somatic mutations: Y loss is observed in about 50% of SCC of males, and loss of the short arm of the inactivated X is common in SCC of females.

**References**


Worsham MJ, Wolman SR, Carey TE, Zarbo RJ, Benninger MS, Van Dyke DL. Chromosomal aberrations identified in culture of squamous carcinomas are confirmed by fluorescence in situ hybridisation. Mol Pathol. 1999 Feb;52(1):42-6


Mandard AM, Hainaut P, Hollstein M. Genetic steps in the development of squamous cell carcinoma of the esophagus. Mutat Res. 2000 Apr;462(2-3):335-42

This article should be referenced as such: