Head and neck cancer: molecular carcinogenesis

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To date it is widely accepted that an accumulation of genetic and epigenetic alterations in oncogenes and tumor suppressor genes forms the basis for the progression of a normal cell to a cancer cell, referred to as the process of multistep carcinogenesis. We are currently beginning to uncover the nature and the sequence of events that are crucial in the development of head and neck squamous cell carcinoma (HNSCC).

HNSCC cells are genetically unstable and display often extensive chromosomal changes, including amplifications, deletions and translocations. The number of genetic alterations is known to increase as the disease progresses when judged by histopathological examination. Evidence is available that in most, if not all, HNSCC, two pathways are impaired: one involving the MDM2 and TP53 genes and one involving CDKN2A (p16), RB1, CCND1 (Cyclin D1) and E2F1. Additional genetic analyses have identified a large number of chromosomal areas, for which most of the gene(s) have not been identified as yet. Genetic alterations associated with the process of head and neck carcinogenesis have potential to be used for improving diagnosis and prognosis, and are currently tested for this purpose.

We have focused on the genetic analysis of the phenomenon of field cancerization in relation to the development of locally recurrent HNSCC and second primary tumors. These studies have led to the proposal of a progression model for HNSCC development [1]. A schematic overview of this model is presented in Figure 1. In the initial phase, a stem cell located in the basal cell layer of the mucosa acquires a genetic alteration; subsequently, a patch is formed, defined as a clonal unit consisting of the stem cell with its daughter cells that all share the DNA alteration. The change of a patch into an expanding field as a result of additional genetic alterations is the next crucial step in this process. This mucosal field push aside the normal epithelium and can expand to a size of >10 cm in diameter. Fields are often macroscopically invisible, but may appear as oral leukoplakia. Ultimately, clonal selection leads to the development of carcinoma within this field of preneoplastic cells. An important clinical implication of this model is that fields often remain after surgery of the primary tumor and may lead to new cancers, which we propose to designate second field tumors (SFT) [2, 3].

The existence of SFT has been proven and they should be considered a separate entity, since they develop from preneoplastic cells clonally related to the initial tumor. They should be discriminated from a recurrent carcinoma that has developed from minimal residual cancer and from a second primary tumor that independently develops from the initial carcinoma. Patients at risk for SFT are an unique patient group for whom intense surveillance is indicated and, in addition, form a target population for chemoprevention (defined as the approach to inhibit, reverse or delay the process of carcinogenesis by administering chemical compounds). The priority is to determine the cancer risk profile of genetically altered fields and identify the genes that drive field cancerization. With this knowledge, highly efficient clinical prevention trials, including those with local application of therapeutics, can be designed.

References

Figure 1. Schematic overview of the proposed concept of carcinogenesis of head and neck squamous cell carcinoma. At the top, the epithelium is shown (green) with the basal cell layer (light orange) including the stem cells (three are shown) and connective tissue (blue). The second stage ("patch phase") shows the formation of a patch (dark orange) as a clonal unit of genetically altered cells. Next, the formation of an expanding field (red) from a patch is visualized. Within such field of genetically altered cells, a more progressed preneoplastic lesion develops (light yellow). In the next stage, that lesion develops into cancer (yellow) and another preneoplastic lesion emerges. The carcinoma is removed by the surgeon, but the field and the preneoplastic lesion remain. At the bottom the development of a second field tumor is shown. This figure was reprinted with permission from Braakhuis et al. [1].