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Review

Oral cancer: Deregulated molecular events and their use as biomarkers

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ABSTRACT

Oral Cancer (OC) is a subset of head and neck cancer (HNC) with an annual worldwide incidence of 275,000 cases. OC remains a significant burden worldwide in terms of diagnosis, treatment and prognosis. Despite desirable outcomes in early diagnosed OCs and treatment advances most OCs are detected in advanced stages. The 5-year survival rate of early-stage disease is ~80% and that of late-stage disease is only ~20%. Recurrence and chemoresistance from a treatment point of view and pain and disfiguration are important factors contributing to the high morbidity and mortality of OC. Furthermore the process of oral carcinogenesis is complex and not yet fully understood. Consequently numerous potential biomarkers have been hypothesised though controversial results across the board hamper their clinical implementation. Of greatest advantage would be biomarkers signalling early events preceeding OC. Biomarker targets predominately involve deregulated molecular events that participate in cell signalling, growth, survival, motility, angiogenesis and cell cycle control but can also use changes in metabolic genes to discriminate healthy form disease state. Promising potential biomarkers include the growth signalling oncogenes, Epidermal Growth Factor Receptor and Cyclin D1, the anti-growth signalling components p53 and p21, apoptotic effectors such as Bcl-2 and also components involved in immortalisation, angiogenesis, invasion and metastasis processes. Translation of these potential biomakers to the patients is closer than ever though few issues remain to be resolved. Firstly large clinical trials are needed to validate their clinical applicability but also standardised methods of collection, storage and processing methods are needed to minimise variability.

Carcinogenic pathways in oral cancer

The use of molecular markers to diagnose oral pre/cancerous lesions is not a new concept. Recent advances in modern screening techniques has opened the door and enabled identification of relevant targets aiming to exploit their potential for early cancer detection. Biomarkers that signal early changes in the epithelium would impact significantly on patients, positively correlating to better prognosis, quality of life and lower treatment costs. The demand for clinically reliable biomarkers has led to a proliferation in the literature of possible targets at genetic, mRNA, protein and metabolome levels, the vast majority of which are intrinsically linked to the aberrant growth of cancer cells. The list of genetic alterations that occur in dysplastic/cancerous cells are numerous, including point mutations, deletions, translocations, amplifications, methylations, microsatellite instability and loss of heterozygosity. Although this growing list of possible biomarkers is extensive, there is currently little transfer of this knowledge into a clinical setting. One example being SaliMark a diagnostic salivary test for Oral Cancer (OC) devised by Elashoff et al. [11] which targets significant changes in seven mRNA and three protein markers identifying patients at risk (see Figs. 1 and 2).

This review summarises the deregulated molecular events occurring in OC and examines their potential as biomarkers.

Self sufficient growth stimulatory signalling

EGFR, HER-2, Her-3, Her-4 and EGF

Signal transduction pathway dysfunction is a focal point in understanding the pathologic route driving cancer. Accordingly epidermal growth factor receptor (EGFR) is one of the most studied oncogenes and an OC treatment target. The EGF family of transmembrane tyrosine kinase receptors includes homodimers or heterodimers of four receptors: EGFR, Her-2, Her-3 and Her-4. Ligand binding triggers autophosphorylation and activation of multiple intracellular signalling cascades including RAS-RAF-MAPK, PI3K/AKT, mTOR, JAK and STAT pathways resulting in a variety of

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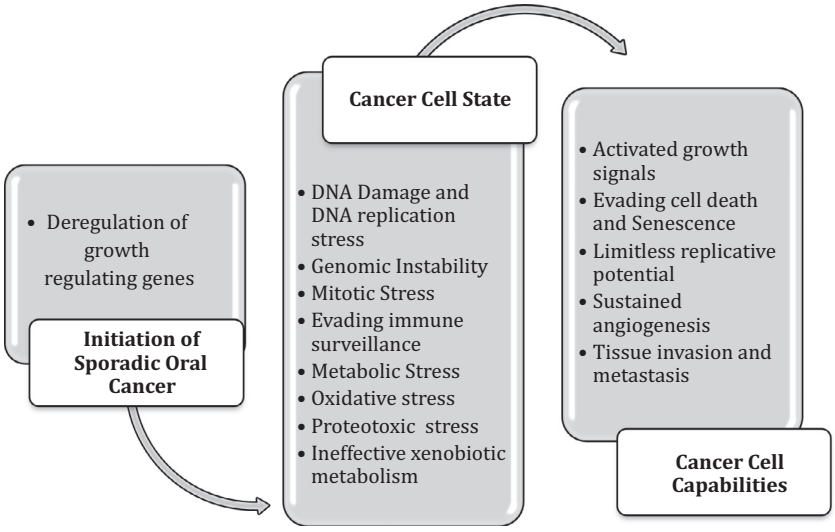

Fig. 1. Hypothesised initiation events in the onset of oral cancer and acquired capabilities of transformed cells.

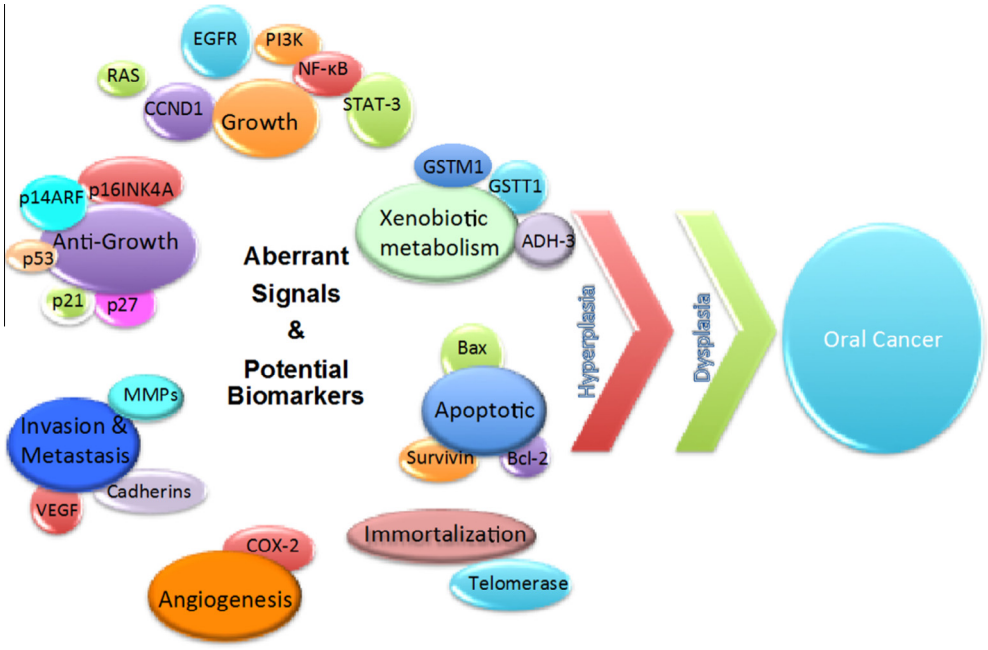

Fig. 2. Summary of a number of deregulated events and their potential use as biomarkers for the detection of OC.

cellular activities including modulation of apoptosis, cell growth, angiogenesis, cell adhesion, cell motility and invasion (see Table 1).

Under basal conditions EGFR is present at low levels on cell surfaces, however in OC an increase of 42–58% in EGFR expression has been reported [18] while 90–100% of all head and neck squamous cell carcinomas (HNSCCs) show increased expression. Its biomarker potential has been strengthened with studies demonstrating high expression of EGFR in leukoplakia lesions associated with OSCC development [21].

Although aberrant EGFR function could be linked to genetic mutations it has been shown that such events are dependent on ethnicity with 0–4% in whites and 7% in Asians [36]. Additional mechanisms of EGFR overexpression are related to the interlinked relationship between EGFR and COX-2, resulting in inhibition of apoptosis and induction of angiogenesis.

Overall EGFR overexpression is considered a hallmark of OC and an independent prognostic marker that correlates with worse prognosis, advanced tumour stage and poor treatment outcome [35]. Clinical application of EGFR was examined using a nano-bio-chip sensor technique in exfoliative cytology specimens targeting both biochemical and morphological changes including EGFR labelling intensity. This study provided a proof of principle showing that increased EGFR in conjunction with cytomorphometry be of predictive value in OC [54].

EGF levels in saliva were examined to determine the prognostic value for leukoplakic lesions and OC [6,15]. Both studies concluded that salivary EGF cannot be used as a biomarker due to failure to detect significant changes between healthy and disease states. However lower salivary EGF levels may indicate a higher susceptibility for OC development [6].