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Cyclin A activity predicts clinical outcome in oral precancer and cancer

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Abstract. Accurate, predictive assessment of the behaviour of oral cancers and precancers remains elusive. Increasing dysregulation of cell proliferation is a feature of carcinogenesis, and alterations in cyclin proteins regulating cell cycle progression are involved in enhanced cell proliferation. The authors of the present study have previously demonstrated increased proliferative activity in oral dysplastic lesions and poorly differentiated carcinomas, and hypothesize that cell proliferation can be used as a predictive agent in clinical management. In this preliminary study, immunohistochemical quantification of cyclin A expression was carried out for 33 excised oral lesions (ranging from mild dysplasia to invasive squamous cell carcinoma, SCC). Clinical outcome was determined as: no disease after 2 years follow-up, persistent disease, or further disease presentation. Labelling Indices (LIs) ranged from 5.5 to 32.1%, and whilst a trend to increased labelling in increasingly dysplastic and neoplastic tissue was seen, this was not statistically significant ($P = 0.06$). High LIs were related to poor clinical outcome ($P = 0.003$), suggesting a definite role for cyclin A measurement as a predictive tool in clinical management.

Keywords: oral cancer; precancer; cyclin A; clinical outcome.

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Oral squamous cell carcinoma (OSCC) remains a lethal disease, characterized by late presentation of locally advanced and destructive tumours of poor prognosis. Despite modern head and neck imaging techniques, detailed histopathological analysis and coordinated multidisciplinary management, it remains impossible to accurately predict clinical outcome for individual patients or tumours.

It is similarly concerning that 5-year survival rates have improved only slightly over recent decades (quoted values ranging from 43 to 59%), despite real advances in both surgery and radiotherapy[4,6]. If improvements in clinical management and patient survival are to occur, better identification of premalignant disease, early intervention in disease progression and improved understanding of how and why cancers develop are required[11].

Oral carcinogenesis is believed to be a multistep process, derived from an accumulation of cellular changes induced by carcinogens, which transform normal epithelium into invasive neoplasms. Fundamental to this process are alterations in genes regulating cell division, cell cycle progression and DNA synthesis and repair. Promotion of oncogenes, inactivation of tumour suppressor genes and alteration of growth factor activity may all lead to abnormal regulation of cell proliferation, which is recognized as fundamental to carcinogenic change[10].

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Initial phenotypic changes in oral mucosa may be recognized histologically as epithelial dysplasia, that varying presence of cellular atypia and tissue dysmaturation that characterizes premalignant disease. Dysplasia is graded as mild, moderate or severe, or as carcinoma-*in situ* (CIS), a continuum of tissue disorganization suggesting a progressively increased risk of malignant change. Unfortunately, histological grading of dysplasia is highly subjective and accurate prediction of which premalignant lesions will develop into carcinoma is not possible by this method, although it is generally assumed that more severely dysplastic lesions are at greatest risk[10,11].

The authors of the present study have previously shown increased epithelial proliferative activity in increasingly dysplastic and neoplastic oral tissue, and hypothesize that cell proliferation could be used as both a prognostic and predictive marker for carcinogenic change and clinical outcome following treatment[9,10].

Incorporating cell proliferation measurement, such as S phase labelling indices, into routine clinical practice remains problematic in view of its time consuming and research laboratory nature, but the use of monoclonal antibodies to proliferation associated antigens in formalin-fixed, paraffin wax archival material offers opportunities to evaluate proliferative labelling as a prognostic indicator in retrospective studies[10].

Alterations in cyclins, the proteins regulating cell cycle progression at various critical checkpoints, are recognized in many human cancers and may be practically useful as surrogate markers of cell proliferation[5,7]. Cyclin A is particularly interesting because it is synthesized during S phase (its appearance coinciding with the onset of DNA synthesis) and is required for both S phase progression and for passage from G2 into mitosis[5,12]. Overexpression of cyclin A may thus be associated with increased proliferative activity, increased populations of S phase cells, rapid cell growth and ultimately tumour development via unbridled cell proliferation[2].

In terms of tumours and their behaviour, high cyclin A labelling has been shown to occur in advanced stage disease, tumours recurring after treatment and those exhibiting lymph node metastases[2].

Studying cell proliferation in oral lesions may be of use not only for prognostic purposes, but also to target more aggressive therapies at lesions exhibiting the highest proliferation indices.

The aim of this preliminary study was to investigate the efficacy of cyclin A as a marker of proliferative activity in a range of dysplastic and neoplastic lesions, and to determine if cyclin A labelling has a role in predicting clinical behaviour in oral carcinogenesis.

Methods

Following local Ethical Committee approval and informed patient consent, a cohort of previously treated oral cancer or precancer patients was randomly selected from the Oncology Database of the University of Newcastle Department of Oral & MaxilloFacial Surgery and invited to take part in the study.

Inclusion criteria required a first presentation of a dysplastic or neoplastic lesion, with no previous history of oral cancer, surgical treatment or radiotherapy, and with complete lesion excision (no positive or involved margins) confirmed by histopathological examination postoperatively.

All patients attended the Oncology/Dysplasia clinic for regular review by the operating clinician and underwent detailed oral examination on each occasion to monitor progress and detect disease. Full details of clinical outcome following surgical excision were recorded for each patient and summarized as: no disease after a 2-year follow-up period, persistent disease (no resolution of disease process), or further disease development. Further disease was defined as local recurrence of oral lesions, development of second primary tumours or cervical lymph node metastases.

Formal histopathological re-examination of archive material was carried out; routinely processed, paraffin-embedded haematoxylin-eosin-stained sections were reviewed to ensure that sufficient, well-orientated tissue was available for study. Dysplasia was graded as mild (atypia confined to the basal third of epithelium), moderate (involving up to two-thirds) or severe (greater than two-thirds), whilst carcinoma-*in situ* (severe tissue dysmaturation extending to an intact basement membrane) and invasive squamous cell carcinoma were also recognized. Twenty non-dysplastic oral biopsy specimens (diagnosed as hyperkeratosis only on microscopy) were included as a control group.

Immunohistochemical detection of cyclin A was performed using a standard avidin–biotin-peroxidase technique following microwave oven antigen unmasking in 10 mM citrate buffer (pH 6.0). Antihuman cyclin A mouse monoclonal antibody at a dilution of 1:50 was used (NCL-CYCLIN A; Novocastra, Newcastle, UK) and the sections counter-stained with thionine.

Tissue samples were analysed using a computer-assisted microscope system that functions by superimposing the computer screen on to the microscope image (Zeiss Axiohome TM interactive microscope; Fig. 1). The base of five successive epithelial ridges or five representative fields of view, depending upon tissue type and organization, were defined for each sample and displayed on both computer screen and microscope eyepiece simultaneously. The cyclin A labelling index (LI%) was determined by counting the number of

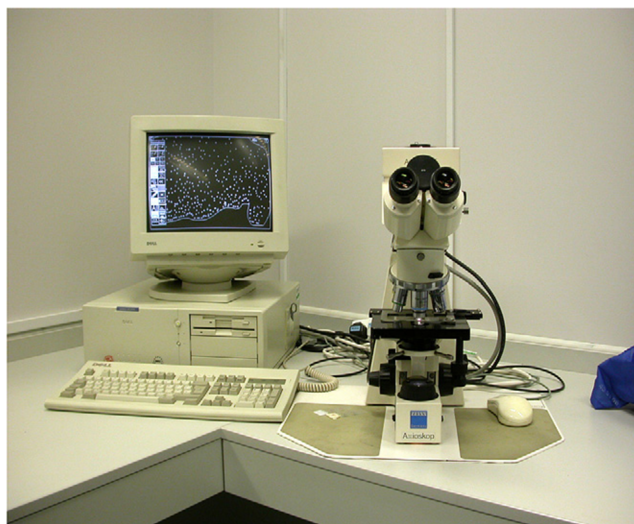

Fig. 1. AxioHome interactive microscope system, showing computer screen analysis of cyclin A-labelled dysplastic epithelium.

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