EXPRESSION OF P٦٣ AND HIF١α IN ORAL EPITHELIAL DYSPLASIA AND ORAL SQUAMOUS CELL CARCINOMA

Thesis submitted to the Faculty of Dentistry, Ain-Shams University for partial fulfillment of the requirements of the Master's Degree in Oral Pathology

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وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ
وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ
عَظِيمًا

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List of Abbreviations

Abbreviation	Word
ARNT	Aryl hydrocarbon receptor nuclear translocator
BHLH	Basic helix loop helix
CBP	CREB binding protein
CDKIs	Cyclin dependant kinase inhibitors
CTAD	C – terminal transactivation domain
DBD	DNA binding domain
E	Embryonic day
FIH	Factor inhibiting HIF
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HIF	Hypoxia inducible factor
INK٤A	Inhibitory kinase
MMP	Matrix metallo-protinease
MDM٢	Murine double minute ٢
NOM	Normal oral mucosa
OD	Oligomerization domain
OED	Oral epithelial dysplasia
OSCC	Oral squamous cell carcinoma
ODD	Oxygen dependant degradation domain
PAI	Plasminogen activator inhibitor
PDGF	Platelet – derived growth factor
PHD	Prolyl hydroxylases
P٦٣-/-	P٦٣ null
SCC	Squamous cell carcinoma
SAM	Sterile alpha motif
SDF	Stromal derived factor
TA	Transactivating domain
TID	Transinhibitory domain
ΔN	Truncated –N terminal domain
VEGF	Vascular endothelial growth factor
VHL	Von Hipple-Lindau

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Introduction

The epidermis is a multi-layered epithelium that protects the living organism from dehydration, mechanical trauma and microbial assaults and is self-renewing throughout the life of the organism. The self-renewing capacity of the epidermis is mediated by multi-potent stem cells which reside in the bulge region of the hair follicle[١], as well as in the interfollicular epidermis.[٢]

Through cell division, epidermal stem cells give rise to daughter stem cells and to transient amplifying cells, after a few rounds of cell division, transient amplifying cells withdraw from the cell cycle and undergo terminal differentiation, a highly reproducible process which results in the expression of unique differentiation markers in each compartment of the epidermis.[٣] However, Genes that are active during normal development of the epidermis are frequently found to be dysregulated during neoplastic transformation.[٤]

Overview on Cancer

Globally the vast majority of malignant neoplasms (٧٥٪) occur in the developing world, where the oral cavity is often the first or second most common site for malignancy[٥] making oral cancer one of the most common cancers in the world.[٦]

Cancer of the oral cavity represents a major health problem. The world wide annual incidence of oral cancers was estimated to be ٢٧٤ ٠٠٠, accounting for ٢,٥٪ of all malignancies in both sexes in ٢٠٠٢.[٧]

Oral Cancer is a class of disease characterized by uncontrolled division of genetically damaged cells and the ability of these cells to spread to adjacent tissues, local lymph nodes, and distant organs.[٨]

The carcinogenic process is graduated and requires the accumulation of multiple genetic alterations in the epithelial cells. These genetic changes generate phenotypic alterations in tumor cells that allow them to continue to survive and expand.[٩]

Mathematical models estimate that approximately seven to ten individual genetic alterations must occur for the development of cancer.[٩]Head and neck cancer is believed to originate via a multistep process that involves the activation of oncogenes and the inactivation of tumor suppressor genes.[١٠]

Most oral cancers are squamous cell carcinomas (SCCs) [١١]. Potential risk factors include, smoking during adolescence that may produce physiologic changes and tobacco carcinogen DNA damage [١٢], and as for never-smokers risk factors are multiple and include alcohol consumption [١٣], human papilloma viral (HPV) infection [١٤], immunosuppression [١٥], history of xeroderma pigmentosum [١٦], and genetic susceptibility, furthermore, there appears to be an increasing population of patients without known risk factors.[١٧]

Review of Literature

Oral Epithelial Dysplasia

As already mentioned SCC is the most common oral cancer and the vast majority of squamous cell carcinomas are preceeded by precursor lesions that can present as either leukoplakia, erthroplakia or erthroleukoplakia.[١١]Microscopically these lesions exhibit oral epithelial dysplasia (OED).

Oral epithelial dysplasia (OED) is a diagnostic microscopic term that is characterized by cellular changes and maturational disturbances indicative of developing malignancy.[١٨]

A diagnosis of OED is important because reported malignant transformation rates among persons diagnosed with OED are as high as ٣٦٪.[١٩]

The histopathological characteristics of epithelial dysplasia include: basal layer hyperplasia, hyperchromatism, loss of intercellular adhesion and normal polarization, abnormal mitoses above the basal cell layer, individual cell keratinization within the spinous layer, cellular pleomorphism, irregular stratification, and altered nuclear-cytoplasmic ratio[٢٠]. Among these histological changes, the presence of basal cell hyperplasia, nuclear enlargement and hyperchromatism and drop-shaped rete-ridges are regarded as the minimal criteria for the histological diagnosis of epithelial dysplasia.[٢١]

OED is graded simply as mild, moderate or severe, by an evaluation of a combination of cytological and architectural changes in the oral epithelium. Mild epithelial dysplasia, shows relatively few cytological aberrations involving only the lower one third of the

epithelium, while at the other end of the scale, severe dysplasia may show significant cytological atypia involving the full thickness of the epithelium and may be designated carcinoma in situ. [٢٢]

Squamous Cell Carcinoma

Over ٩٠٪ of head and neck cancer are squamous cell carcinomas.[٢٣] Median age at presentation is ٦٠ years, and two thirds of patients are men. There is a strong association with alcohol or tobacco use.[٢٤] SCC typically presents as a persistant mass , nodule, or indurated ulcer. Colour changes are common and consist of red or red and white hues. Involvement of adjacent tissues is possible, though not necessary, and represents local invasion of the tumor. Symptoms are uncommon in earlier stages of the disease but become frequent with advanced local invasion. In particular parasthesia and anesthesia in the absence of a history of trauma are highly suggestive of an invasive malignancy. The majority of intra-oral squamous cell carcinomas originate from non-keratinized mucosa. The three most common sites of involvement are the tongue (٣٠٪), lip (١٧٪), and floor of the mouth (١٤٪).[٢٥] Recently, a trend towards increased numbers of lesions arising from the gingiva was reported. [٢٦]

Histopathologically SCC is characterized by invasion of malignant epithelial islands and cords in the underlying connective tissue through the basement membrane, the squamous cells display the features of epithelial dysplasia, some cells are seen scattered in the connective tissue individually. There`s a strong inflammatory or immune cell response to the invading epithelium, the normal product of squamous cells is keratin and keratin pearls are produced within lesional epithelium together with other signs of dysplasia, the lesions