IMMUNOHISTOCHEMICAL EXPRESSION OF CD44 AND MMP-9 IN ORAL SQUAMOUS CELL CARCINOMA

Thesis

submitted to the Faculty of Dentistry-Ain Shams University for partial Fulfillment of the requirements for the Master Degree in Oral Pathology

By

Melad Abdullah Al-Swehly

(B.D.S)

Faculty of Dentistry
Tripoli University

1993

Faculty of Dentistry
Ain –Shams University
2015

SUPERVISORS

DR. Mohamed Salah Eldin Ayoub
Professor of Oral Pathology
Faculty of Dentistry
Ain Shams university

DR. Mohamed Hossam Eldin Elmalahy
Professores of Oral Pathology
Faculty of Dentistry
Ain Shams university

بسم الله الرحمن الرحيم

Acknowledgement

I would like to express my deepest gratitude and appreciation to **Prof.Dr.Mohamed Salah El-Din Ahmed Ayoub,** professor of oral pathology, faculty of Dentistry, Ain-shams University, for his constant supervision, guidance and for allowing me to benefit from his vast knowledge.

I would also like to convey special thanks and recognition to **Dr.Mohamed Hossam Eldin Elmalahy,** Professors of Oral Pathology faculty of Dentistry-Ain Shams university, who has given me continuous encouragement and exceptional assistance.

Last but not least, Imust thank my dear friend **Dr.Salem Badree** for his help and support. God bless him.

Dedications

To the spirit of my father

Spirit of my mother

My dear wife

And my lovely children

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List of Abbreviations

AA: amino acid

ANOVA: analysis of variance

CD44: cluster of differentiation

CD44s: standard CD44

CD44v: variant CD44

CNS: central nervous system

CSCs: cancer stem cells

DAB: diamino benzidine

DNA: deoxyribonucleic acid

ECM: extracellular matrix

EGF: epidermal growth factor

EGFR: epidermal growth factor receptor

EMT: epithelial-mesenchymal transition

ERM: ezrin,radixin, and moesin

HA: hyaluronic acid

HNSCC: head and neck squamous cell carcinoma

HPV: human papiloma virus

MAF: mean area fraction

MDSCC: moderate differentiated SCC

MMPs: matrix metalloproteinases

MMP-9: matrix metalloproteinase-9

MMPIs: matrix metalloproteinase inhibitors

MT-MMPs: membrane type- MMPs

OSCC: oral squamous cell carcinoma

PBS: phosphate buffered saline

PDSCC: poorly differentiated SCC

RNA: ribonucleic acid

SCC: squamous cell carcinoma

SD: standard deviation

TI-MMPs: tissue inhibitors-MMPs

WDSCC: well differentiated SCC

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Introduction and review of literature

Oral cancer is the sixth most common cancer worldwide [(1)]. More than 90% of all oral cancers are squamous cell carcinoma (SCC)[(2, 3)]. The most important risk factors for oral SCC are use of tobacco or betel quid and the regular drinking of alcoholic beverages. However, infection with high-risk human papilloma virus (HPV) genotypes, and a diet low in fresh fruits and vegetables have also recently been implicated in the aetiopathogenesis of oral SCC [(1, 4)].

The highest incidence and prevalence of oral SCC is found in the Indian subcontinent where the risk of developing oral SCC is increased by the very prevalent habits of chewing tobacco, betel quid and areca-nut[(2)].

The mutagenic effects of tobacco, alcohol, betel quid or areca-nut are dependent upon dose, upon frequency and upon duration of use, and are accelerated and exaggerated by the concurrent use of two or more of these agents[(4)].

The survival index continues to be small (50%), as compared to the progress in diagnosis and treatment of other malignant tumors. According to World Health Organization, carcinoma of oral cavity in males in developing countries, is the sixth commonest cancer after lung, prostrate, colorectal, stomach and bladder cancer, while in females, it is the tenth commonest site of cancer after breast, colorectal, lung, stomach, uterus, cervix, ovary, bladder and liver[(5)].

Oral squamous cell carcinoma (OSCC) remains a major public health problem world-wide, with ~275,000 cases annually and little improvement in survival rates[(6)].

Despite advances in treatment, facial disfigurement, and functional disturbances including mastication, swallowing, and speech remain distressingly common [(7)].

It is critical to understand key molecular mechanisms in the transformation and spread of OSCC, with a view to designing targeted- or individualized therapies [8, 9].

The stage of oral SCC at the time of diagnosis is the most important prognostic factor [10]. OSCC is most frequently diagnosed late in the course of the disease because affected persons fail to seek professional advice timeously, either because they do not understand the significance of early signs and symptoms, or because they are ignorant of the health implications [11].

OSCC arises by malignant transformation of a single precursor cell which by clonal expansion gives rise to a monoclonal cancer cell population. It appears that the precursor cancer cells possess the capacity for relatively unlimited self-renewal but have a limited rate of apoptosis with the outcome of longevity and the ability to initiate and sustain the ongoing growth of the cancerous tissue [12, 13].

The origin of the precursor cell which gives rise to OSCC is uncertain. It is likely that it arises, as is the case in other cancers, from a tissue-specific stem cell or its progenitor cell, which has acquired epigenetic and/or genetic alterations [14, 15]. However, it is also possible that the OSCC precursor cell may have arisen from a stem cell which has acquired a precancerous phenotype during embryogenesis and has then differentiated into a tissue-specific cancer stem cell [16, 17].

Another possibility is that the OSCC precursor cell originates from a mature keratinocyte which has undergone cytogenetic alterations resulting in its dedifferentiation into the analogue of an immature progenitor/stem cell which can express the dysregulated intracellular pathways and transcription factors of a tissue-specific cancer stem cell phenotype [18, 19].