Retinoic acid receptor β expression in oral pre-cancer progression: A marker for Carcinogenesis and early intervention

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Introduction & Background:

The cancer epidemic is due to the combined effect of the ageing of populations, and the high or increasing levels of cancer risk factors. The burden of OSCC is huge because of the permanent impairment, high mortality and associated high cost of treatment. OSCC is often preceded by oral pre-cancer lesions/ conditions (PMDs). Presently there are no reliable biomarkers that can offer preventive/therapeutic management for malignant potential of oral pre-cancer lesions. Retinoic Acid (RA) has been identified as a regulator of cell proliferation, differentiation and apoptosis and thus is critical for tissue morphogenesis and homeostasis. Retinoic Acid pathway involves numerous genes that control its functioning. Amongst them RAR β is the important one which deals with mechanism of RA effect on cell and body as a whole. Retinoic acid signalling has been reported as aberrant in many types of cancer. Considering that RARs are the mediators of RA-signalling, studying tissue specific receptor expression could potentially be an effective means of detecting aberrant signalling and early diagnosis in oral carcinogenesis.

Methods & Materials:

20 oral precancer tissue samples and 10 normal oral tissue samples were selected based on inclusion and exclusion criteria of the study. Amongst the 20 oral precancerous samples, 10 were in mild, 5 moderate and 5 were in severe histopathological grade (WHO classification). All tissue sample were immunostained with Retinoic Acid Receptor β primary and secondary antibody. Staining was graded by two independent pathologists and an average of their readings was taken.

Oral cancer and oral pre cancer To define anatomically, oral cancer is a malignant neoplasia arising on lips, the lining inside the cheeks and lips, the anterior two thirds of the tongue, the upper and lower gingiva, the floor of the mouth under the tongue, the roof of the mouth, and the small area behind the third molar. Oral cancer is the 2nd most common cancer in India amongst men (11.28% of all cancers), 5th most frequently occurring cancer amongst women (4.3% of all cancers) and the 3rd most frequently occurring cancer in India amongst both men and women [3]. It has been well-described in the literature that virtually all oral cancers are preceded by visible clinical changes in the oral mucosa usually in the form of white or red patch (two-step process of cancer development). WHO in 1978 used the term 'precancer' which was further classified into 'lesions' and 'conditions' a) A precancerous lesion is "a morphologically altered tissue in which oral cancer is more likely to occur than its apparently normal counterpart." These precancerous lesions include leukoplakia, erythroplakia, and the palatal lesions of reverse smokers. b) A precancerous condition is "a generalized state associated with significantly increased risk of cancer." The precancerous conditions include submucous fibrosis, lichen planus, epidermolysisbullosa, and discoid lupus erythematous.

Importance of vitamin A pathway:

Oral cancer chiefly involves non- keratinized stratified squamous epithelium. It was observed that these nonkeratinizing squamous cells can undergo keratinization in vivo during vitamin A deficiency, indicating that the maintenance of the nonkeratinizing state of squamous cells depends on the continuous presence of Retinoic acid/ Vitamin A. Retinoids exert profound effects on the growth and differentiation of normal and malignant epithelial cells, also Vitamin A and its analogues delay tumour appearance, retard tumour growth and regress tumours. It was observed that retinoids suppress the proliferation of head and neck cancer cells in monolayer cultures and inhibit the formation of colonies in semisolid agarose and decrease the growth of multicellular spheriods. In addition, retinoids also suppress the differentiation markers K1 keratin, type 1 transglutaminases and involucrin.

Results:

Expression of Retinoic Acid Receptor β (RAR β) was highest in normal oral tissues and which decreased from mild to severe histopathological grades in oralprecancer cases. The decrease in expression of RAR β correlated with histopathological progression of oral precancer.

Discussion:

Since RAR β is involved in RA signalling and its bioavailability, its loss is anticipated during carcinogenesis. Infact, many studies have reported that RAR β expression is lost early in carcinogenesis or is epigenetically silenced in many solid tumors. Our findings are amongst first few studies in oral precancer cases where downward expression of RAR β has been reported during carcinogenesis process.

Conclusion:

Loss of RAR β expression in oral precancer progression can provide an opportunity for novel treatment strategies to be investigated using retinoids together with epigenetic modifiers that promote re-expression of silenced genes specially at the precursor level.

However inconsistent results observed in various studies required a detailed insight into the underlying metabolic mechanism. Evidence for PRAME overexpression in oral cancers and its dominance in repression of Retinoic acid binding to its receptor has provided a partial explanation for the paucity of therapeutic successes with retinoids in the past. In chemoprevention, selection of patients with PRAME-negative premalignant lesions for retinoid-based preventive treatments might result in better clinical responses. Considering the role of PRAME in the RA metabolism, it is suggested that only patients with the premalignant lesions negative for PRAME are likely to be responsive to retinoid therapy and may be the best potential candidates for chemoprevention with retinoids.

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