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Aniket Adhikari *

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Mini Review

Co- relation between Oral Cancer Biomarker (Micronuclei) and Human Group 1 Carcinogen (Betel Quid) through Sonic Hedgehog Signaling pathway: A Mini Review

Aniket Adhikari *

Vivekananda Institute of Medical Sciences. (V.I.M.S), Department of Genetics, Ramakrishna Mission Seva Pratishthan (RKMSP) 99, Sarat Bose Road, Kolkata.

***Correspondence Author:** Aniket Adhikari, Vivekananda Institute of Medical Sciences (V.I.M.S) Department of Genetics, Ramakrishna Mission Seva Pratishthan (RKMSP) 99, Sarat Bose Road. Kolkata.

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Abstract

Hedgehog signaling pathway is one of the prime regulators of cell growth and differentiation during embryogenesis. Aberrant expression of sonic hedgehog signaling leads to oral squamous cell carcinoma and suggest that this pathway mediates its tumorigenesis. The International Agency for Research on Cancer (IARC) has listed betel quid as group 1 human carcinogenic agents, which have role in multistage progression in oral squamous cell carcinoma. Oral squamous cell carcinoma is characterized by formation of micronuclei (MN) with higher percentage in cancer and pre cancer (in betel quid chewers) cases than normal. MN assay is noninvasive, painless assay for oral cancer and pre-cancerous patients. The present review focuses on carcinogenic effects of betel quid on increasing percentage of MN (important oral cancer biomarker).

Keywords: micronuclei (mn); betel quid (bq); sonic hedgehog pathway (shh); oral squamous cell carcinoma (oscc)

Introduction

Hedgehog signaling cascade plays a major role in many processes like cell differentiation and organ formation during normal vertebrate embryonic development, this pathway is important to the maintenance of adult stem cells [1]. The name hedgehog has been derived from the polypeptide ligand called Hedgehog (Hh) found in fruit flies of the genus Drosophila. This pathway was first discovered in 1980 by Christiane Nüsslein-Volhard and Eric Wieschaus [2]. Studies have shown that three members of this family are present in mammals: Sonic hedgehog (SHH), Desert hedgehog (DHH) and Indian hedgehog (IHH), all of which encode secreted proteins [3]. Some groups have suggested that certain signaling pathways, such as sonic hedgehog (SHH) and wingless type (WNT) are associated with carcinogenesis and, consequently, mediate the initiation and progression of human malignant tumors [4,5]. The SHH pathway is one of the most important pathways in vertebrates, regulating many processes during embryonic development, and oral mucosa [6].

Three well-known pathways such as Wnt, Notch and Hedgehog (Hh) play an important role in the development and normal homeostasis. Schneider et al. assessed the expression of SHH signaling proteins in head and neck squamous cell carcinoma HNSCCs, he failed to note any expression of SHH signaling proteins in oral normal mucosa.[7]. Wang et al. in 2012, found overexpression of SHH in OSCC.[8] Yue et al. suggested that the SHH/Gli pathway may be critical for SCC recurrence including metastasis [9].

Oral squamous cell carcinoma (OSCC) is the most common malignancy in the head and neck region, accounting for about 2,60,000 new cases and 1,24,000 OSCC-related deaths worldwide annually.[10] According to the study carried out by the National Institute of Public Health (Japan), 86% of the world's oral cancer victims reside in India. The scenario of oral cancer ranks number one among men and third among women.[11]. Oral cancer is among the top three types of cancers in India.

Severe alcoholism, use of tobacco like cigarettes, smokeless tobacco, betel nut chewing common risk factors for oral cancer. The incidence of oral cancer is highest in India, south and South East Asian countries. In India, 90 -95% of the oral cancers is squamous cell carcinoma. The international agency for research on cancer has predicted that India's incidence of cancer will increase from 1 million in 2012 to more than 1.7 million in 2035. This indicates that the death rate because of cancer will also increase from 680000 to 1-2 million in the same period. More than 90% of OC cases report using tobacco products. The forms of tobacco are use of smokeless tobacco, use of betel liquid, pan (pieces of Areca nut), processed or unprocessed tobacco, aqueous calcium hydroxide (slaked lime) and some pieces of are a nut wrapped in the leaf of piper betel vine leaf. [12]

Micronuclei (MN) are the small extra nuclei which are formed in metaphase and anaphase stage. The presence of micronuclei reflects a genotoxic and carcinogenic exposure. In general, micronucleus analysis is utilized in both genotoxicity testing with its exposure which effects in human population.

These MN assay allows the detection of both aneugenic agents (numerical chromosome alterations) and clastogenic agents (chromosome breakage). Chromosome breakage and mitotic apparatus dysfunctions are involved in the morphogenesis of MN, closely associated with chromosome instability [13]. The frequency of micronucleated exfoliated cell elevates in human tissues, which appear to be the main targets of carcinogens and from which the carcinomas arise.

Micronuclei are induced in oral exfoliated cell by a variety of carcinogenic substances which is found in tobacco, betel nut and alcohol. Tobacco specific nitrosamines {N- nitrosoanabasine (NAB), 4-(N- methyl-N- nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)} have been reported to a potent clastogenic and mutagenic effect which are responsible for the induction of chromatid / chromosomal aberrations resulting in the production of [14].

In our study total 311 subjects were screened from different areas of Eastern part, North- Eastern part of India (Silchar, Shillong) and also from RKMSP Hospital, Kolkata. 61.09% had betel quid chewing habit (mainly 35- 59 years old person). Percentage of micronuclei is higher than the normal in precancerous cases such as (3.9 folds) in (leukoplakia, erythroplakia, Oral submucous fibrosis) and cancerous cases (5.3 folds) in (OSCC), who had betel quid chewing habit (10 to 15 BQ / day in the last 4-5 years).

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