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Decoding oral cancer conundrums from 'bad luck' point of view

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Carcinogenesis is characterized by accumulation of genetic mutations in the cells. It is said that once the threshold level is reached, cells get transformed into a malignant state. Unfortunately, nobody knows what this threshold level of genetic mutations constitutes. With advancement in technology, researchers have made significant strides in understanding various facets of genetic mutations in carcinogenesis. Initially, genetic mutations in carcinogenesis were thought to be arising from environmental factors. Later, some heritable genetic mutations were identified in the genes that are directly or indirectly responsible for malignant transformation of cells. Such diseases are called 'inherited cancer syndromes'. Many such syndromes have been found to be associated with oral squamous cell carcinoma (OSCC) [1]. Vast accumulation of knowledge about environmental and hereditary genetic mutations have opened up the avenue for prediction and management of malignant neoplasms. However, recently, a third type of genetic mutation has been reported to be associated with carcinogenesis and is called the R mutation [2]. These mutations occur in normal cells during natural DNA replication of cell division. It has been observed that there are on an average three R mutations occurring per cell division which could be due to quantum effect on base pairing, polymerase mistakes, hydrolytic deamination of bases and endogenous reactive species [3]. The most interesting fact about it is that one cannot expect and prevent these mutations. Intriguingly, recently it has been observed that 66% of the mutations in cancers are attributed to R mutations followed by 29% to the environment and 5% to hereditary [4]. These results are based on a mathematical model proposed by Tomsetti *et al.* [4], which is viewed skeptically by many cancer researchers. Since random and unavoidable R mutations are independent of any governing or controlling factors, many investigators labeled them as 'bad luck' mutations.

OSCC is the most common malignant neoplasm oral cavity, which arises from stratified squamous epithelium. Recent technological advances have made significant strides in understanding some of the intricate mechanisms of tumor initiation and progression. However, some OSCC conundrums still remain unanswered in the literature.

Myriads of oral potentially malignant disorders (OPMDs) precedes OSCC [5]. This is one of the unique aspects of OSCC which differentiate it from other malignancies of the body. Prediction of malignant transformation rate of OPMDs has always been the main focus of work for many researchers across the globe. However, even after making progress in technical advancements, there is still no marker (clinical, radiological or molecular) available in clinical practice for accurate determination of malignant potential of an OPMD [6]. As mentioned earlier, R mutations, which are random, unavoidable and nonpredictable, play an important role in malignant transformation. If we apply this to OPMDs, then it would be impossible to predict the malignant transformation potential of any lesion of the oral cavity. This could perhaps be the reason why there is still no single reliable predictive marker available. It also raises a doubt on whether we should stop further exploring the malignant potential of OPMDs. Then the only option which remains is the early detection and management of the patients.

It is a known fact that OSCC usually occurs at the site of OPMDs. As previously described, a premalignant lesion is a morphologically altered state in which cancer is more likely to occur than its normal counterpart [7]. Carcinogenic attack is concentrated at the site of OPMD, and hence malignancy occurring at the site of OPMD is quite conceivable. But occurrence of malignancy at the site other than OPMD, which is a reality [8], is quite intriguing and not successfully and convincingly introspected in the literature. We believe that R mutations could be the answer to this question. Even if environmental factors are acting at a particular site in the oral cavity leading to OPMD, the R mutations at some other site (away from the OPMD) could be dominant enough to produce malignancy.

OSCC has always been regarded as a habit-associated cancer. However, nonhabit (nontobacco, nonalcohol and non-HPV) associated OSCC is not an uncommon entity [9,10]. Many attempts have been made in the literature to understand the pathogenesis behind carcinogenesis of such OSCC [11,12]. Still today, no substantial conclusions have been reached on this issue. R mutations are independent of any external (carcinogens) or internal (hereditary) factors, and their involvement in nonhabit-associated OSCC is highly conceivable. Future research in this regard will unveil the mystery behind this unusual variant of OSCC.

The fact that cancer occurs more commonly in certain tissues can be explained by stem cell division [2]. In the USA, the lifetime risks of cancer between different tissues were found to be strongly correlated with total normal stem cell divisions [2]. It is widely documented that around three mutations occur every time a normal human stem cell divides [13,14]. The cause of this correlation is thought to be the driver gene mutations that randomly result from the divisions. The idea that the rate of normal cell division controls cancer risk in many tissues has been shown by recent mouse models [15].

Time required to replace all the cells in the epithelium is known as turnover time. It is obtained by estimating the time taken by a cell to divide and pass through the entire epithelium. Ultimately, turnover time actually represents the stem cell division activity in the basal cell layer. Intriguingly, oral mucosa shows site-specific variation in epithelial turnover rate [16]. The turnover time has been estimated to be 41–57 days in gingiva, 24 days in hard palate, 20 days in floor of mouth, 14 days in buccal mucosa and 5–6 days in junctional epithelium [16,17]. Turnover time for tongue is not yet investigated in the literature.

According to the global statistics, the buccal mucosa and tongue are the most common sites for OSCC. The tongue is the most common site among European and the US populations, amounting to 40–50% of oral cancers and buccal cancer is more common among Asian population [18]. The reason for this has been bestowed to the practice of tobacco and alcohol consumption habit (environmental factor). Relatively, other intraoral sites for OSCC are not very common which include floor of the mouth, gingiva and palate. If we think in terms of R mutations, the buccal mucosa (less turnover time, i.e., more stem cell divisions) is justified as the most common site for OSCC. Although turnover rate is not available for tongue OSCC, we believe the same could also be applicable to it.

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