Potential Role of Tumor Microenvironment in the Progression of Oral Cancer

The stromal cells adjacent to the tumor including the fibroblasts, inflammatory cells, lymphatic and vascular endothelial cells constitute the ‘tumor microenvironment’ (TM). Recent in vivo and in vitro studies have emphasized the role of stromal components on the growth, differentiation and invasiveness of the tumor cells. In addition, vascular, lymphatic or perineural invasion have proven to have independent prognostic value. Despite the compelling evidence correlating the TM with the initiation and progression of cancer, our knowledge on the role of the genes mediating the various cellular interactions in the tumour struma is limited. Bhowmick et al. in 2004 demonstrated the initiation and progression of prostrate and gastric epithelial tumors, following the inactivation of transforming growth factor-β type II receptors in the stromal fibroblast. Multiple genetic abnormalities including loss of heterozygosity was noticed in tumor stromal cells. Toll-like receptors (TLRs) represent a group of inflammatory mediators transmitting signals between the stromal cells of TM. The exact role of TLRs in tumorigenesis remains controversial. Study conducted by Ng et al. showed a greater TLR2 expression on the TM cells of oral squamous cell carcinoma and dysplasia in comparison to TM cells of hyperplasia. Apetoh et al. observed that an increased expression of TLRs enhanced maturation of the antigen-presenting cells, inhibiting tumor growth. Califano et al. suggested that TLR-induces cancer cell apoptosis, thus hindering tumor progression. Lotze et al. in 2007 proposed that increased TLRs in tumour stroma may hinder the host’s antitumor property by responding to the DAMPS released from the necrotic/injured cancer cells. Orimo et al. observed that the tumour-associated fibroblast (TAF) produced higher levels of stromal-derived factor, enhancing tumor angiogenesis through additional recruitment of endothelial progenitor cells. Oyama et al. in their study illustrated a consistent rise in the fibronectin containing extradomain EDA, EDB and IIICS. Fibronectin-EDA is essential for the development of myofibroblasts and fibronectin-EDB is responsible for tumor neovasculature. MMPs role in tumor progression is recently challenged by a study conducted by Gutierrez-Fernandez et al. They observed that MMP-8 suppressed metastasis by modulating tumor cell adhesion and invasion. Hypoxia in the TM is proven to be an independent prognostic factor. It stimulates the release of hypoxia inducible family proteins (HIF). Hypoxia inducible family proteins modulates cell proliferation, apoptosis, angiogenesis and tissue remodelling. Various immunomodulatory mediators including inflammatory cells influence tumor progression by modulating the host immune response. Tumour-associated macrophages (TAMs) are found consistently elevated in TM. TAMs promote tumor growth by releasing epidermal growth factor and vascular endothelial growth factor which in turn produce cytokines and enzymes responsible for tumor invasion, angiogenesis and metastasis. Cancer cells due to their genetic instability are less susceptible to targeted gene therapy. The cells of the TM are relatively stable and are less likely to acquire any resistance to therapeutic interventions. Thus, studies aiming at isolating and characterizing these TM cells may provide us with more responsive molecular targets and allow us to understand the complex molecular interactions between tumor cells and their microenvironment.

REFERENCES


Shankargouda Patil
Associate Professor
Department of Oral Pathology
Faculty of Dental Sciences
MS Ramaiah University of Applied Sciences
Bengaluru, Karnataka, India

Roopa Rao
Professor and Head
Department of Oral Pathology
Faculty of Dental Sciences
MS Ramaiah University of Applied Sciences
Bengaluru, Karnataka, India

Thirumal Raj
Final year postgraduate Student
Department of Oral Pathology
Faculty of Dental Sciences
MS Ramaiah University of Applied Sciences
Bengaluru, Karnataka, India