Editorial

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).[1] 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.[2] 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 stroma is limited.[2,3] Bhowmick et al[4] 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.[4] 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 tumerigenesis remains controversial. Study conducted by Ng et al[5] 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 al6 and Szczepanski et al[7, 8] observed that an increased expression of TLRs enhanced maturation of the antigen-presenting cells, inhibiting tumor growth. Califano et al,[9] Tsui el al,[10] and Sheu et al[11] suggested that TLR-induces cancer cell apoptosis, thus hindering tumor progression. Lotze et al[12] 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[13] observed that the tumour-associated fibroblast (TAF) produced higher levels of stromal-derived factor, enhancing tumor angiogenesis through additional recruitment of endothelial progenitor cells.[13] 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.[14,15] MMPs role in tumor progression is recently challenged by a study conducted by Gutierrez-Fernandez et al.[16] 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.[17-19] Various immunomodulatory mediators including inflammatory cells influence tumor progression by modulating the host immune response.[1] 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.[20-22] 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

1. Lorusso G, Rüegg C. The tumor microenvironment and its contribution to tumor evolution towardmetastasis. Histochem Cell Biol 2008 Dec;130(6):1091-1103.
2. Allinen M, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, et al. Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell 2004 Jul;6(1):17-32.
3. Kapse SC, Rathod N, Baad R, Mandlik J, Sharma AS, Bommanavar S. Quantitative assessment of myofibroblast in severe dysplasia, microinvasion andoral squamous cell carcinoma: an immunohistochemical study. J Contemp Dent Pract 2013 Jan;14(1):34-38.
4. Bhowmick NA, Chytil A, Plieth D, Gorska AE, Dumont N, Shappell S, Washington MK, Neilson EG, Moses HL. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacentepithelia. Science 2004 Feb 6;303(5659):848-851.
5. Ng LK, Rich AM, Hussaini HM, Thomson WM, Fisher AL, Horne LS, Seymour GJ. Toll-like receptor 2 is present in the microenvironment of oral squamous cell carcinoma. Br J Cancer 2011 Feb;104(3):460-463.
6. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, Mignot G, Maiuri MC, Ullrich E, Saulnier P. Toll-like receptor 4-dependent contribution of the immune system to anticancerchemotherapy and radiotherapy. Nat Med 2007 Sep;13(9):1050-1059.
7. Szczepanski MJ, Czystowska M, Szajnik M, Harasymczuk M, Boyiadzis M, Kruk-Zagajewska A, Szyfter W, Zeromski J,Whiteside TL. Triggering of Toll-like receptor 4 expressed on human head and neck squamous cell carcinoma promotes tumor development and protects the tumor from immune attack. Cancer Res 2009 Apr;69(7):3105-3513.

8. Szczepanski MJ, Stelmachowska M, Stryczynski L, Golusinski W, Samara H, Mozer-Lisewska I, Zeromski J. Assessment of expression of toll-like receptors 2, 3 and 4 in laryngeal carcinoma. Eur Arch Otorhinolaryngol 2007 May;264(5):525-530.
9. Califano J, Riet PVD, Westra W, Nawroz H, Clayman G, Piantadosi S, Corio R, Lee D, Greenberg B, Koch W,Sidransky D. Genetic progression model for head and neck cancer: Implications for field cancerization. Cancer Res 1996 Jun;56(11):2488-2492.
10. Tsui IF, Rosin MP, Zhang L, Ng RT, Lam WL. Multiple aberrations of chromosome 3p detected in oral premalignant lesions. Cancer Prev Res (Phila) 2008 Nov;1(6):424-429.
11. Sheu JJ, Hua CH, Wan L, Lin WJ, Lai MT, Tseng HC, Jinawath N, Tsai MH, Chang NW, Lin CF, et al. Functional genomic analysis identified epidermal growth factor receptor activation as the most common genetic event in oral squamous cell carcinoma. Cancer Res 2009 Mar;69(6):2568-2576.
12. Lotze MT, Zeh HJ, Rubartelli A, Sparvero LJ, Amoscato AA, Washburn NR, Devera ME, Liang X, Tor M, Billiar T. The grateful dead: damage-associated molecular pattern molecules and reduction/oxidation regulate immunity. Immunol Rev 2007 Dec; 220:60-81.
13. Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/ CXCL12 secretion. Cell 2005 May;121(3):335-348.
14. Oyama F, Hirohashi S, Sakamoto M, Titani K, Sekiguchi K. Coordinate oncodevelopmental modulation of alternative splicing of fibronectin pre-messenger RNA at ED-A, ED-B, and CS1 regions in human liver tumors. Cancer Res 1993 May;53(9):2005-2011.
15. Serini G, Bochaton-Piallat ML, Ropraz P, Geinoz A, Borsi L, Zardi L, Gabbiani G. The fibronectin domain ED-A is crucial for myofibroblastic phenotype induction by transforming growth factor-beta1. J Cell Biol 1998;142(3):873-881.
16. Gutiérrez-Fernández A, Fueyo A, Folgueras AR, Garabaya C, Pennington CJ, Pilgrim S, Edwards DR, Holliday DL, Jones JL, Span PN. Matrix metalloproteinase-8 functions as a metastasis suppressor through modulation of tumor cell adhesion and invasion. Cancer Res 2008 Apr;68(8):2755-2763.
17. Chen CL, Chu JS, Su WC, Huang SC, Lee WY. Hypoxia and metabolic phenotypes during breast carcinogenesis: expression of HIF-1, GLUT1, and CAIX. Virchows Arch 2010 Jul;457(1):53-61.
18. Carmeliet P, Dor Y, Herbert JM, Fukumura D, Brusselmans K, Dewerchin M, Neeman M, Bono F, Abramovitch R,Maxwell P, et al. Role of HIF-1 in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature 1998 Jul;394(6692):485-490.
19. Canning MT, Postovit LM, Clarke SH, Graham CH. Oxygen-mediated regulation of gelatinase and tissue inhibitor of metalloproteinases-1 expression by invasive cells. Exp Cell Res 2001 Jul;267(1):88-94.
20. Lewis JS, Landers RJ, Underwood JC, Harris AL, Lewis CE. Expression of vascular endothelial growth factor by macrophages is up-regulated in poorly vascularized areas of breast carcinomas. J Pathol 2000 Oct;192(2):150-158.
21. O'Sullivan C, Lewis CE, Harris AL, McGee JO. Secretion of epidermal growth factor by macrophages associated with breast carcinoma. Lancet 1993 Jul;342(8864):148-149.
22. Sica A, Saccani A, Bottazzi B, Polentarutti N, Vecchi A, van Damme J, Mantovani A. Autocrine production of IL-10 mediates defective IL-12 production and NF-κB activation in tumor-associated macrophages. J Immunol 2000 Jan;164(2):762-767.

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