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EDITORIAL

Antiangiogenic Therapy in Oral Cancer: A Thoughtful Consideration

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Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm of oral cavity, which is usually preceded by premalignant disorders.[1,2] Despite recent advances in surgery, radiation, and chemotherapy, prognosis of OSCC remains dismal with minimal improvement seen in the last few decades. Reason could be attributed to the extraordinary uniqueness shown by OSCC in comparison with other carcinomas of the body.[3] Even the metabolism of chemotherapeutic and targeted drugs is different in OSCC patients.[4] It is generally agreed that understanding of the molecular mechanisms underlying the pathogenesis and progression of OSCC is crucial for the development of more rational and successful techniques for effective treatment.[5] One of the recent advancements in cancer therapeutics is targeted drug therapy.[6] Various molecules that play a vital role in carcinogenesis have been targeted to develop effective treatment strategies.[7,8] Although the advancement in this direction is very fast, it is still in infancy stage.

Angiogenesis is the hallmark of carcinogenesis and plays a very important role in cell survival and metastasis. Many angiogenic markers have been found to be elevated in cancer and displayed direct prognostic relevance. Hence, angiogenesis-related markers have been considered as very encouraging potential therapeutic targets for cancer treatment. Among all the markers, vascular endothelial growth factor (VEGF) plays a very important role in new blood vessel formation and its role in oral cancer is very well known. The VEGF family of proteins consists of seven ligands, including VEGF A–E and placenta growth factor 1 and 2, which show affinity for various types of VEGF receptors.[9] Antiangiogenic therapy is making tremendous advancement in drug development, which can stop the events in process of tumor angiogenesis. Different antiangiogenic drugs currently under investigation are listed in Table 1. We believe that "factors" and "receptors" are not the only game changers in tumor angiogenesis but there are many crucial events that are needed to be taken into consideration for successful implementation of anti-angiogenic therapy which is discussed in this editorial.

Micro-RNA (miRNA) and related therapeutic approaches hold great promise in the field of cancer management.[10] One of the most promising prospects is miRNA that regulates angiogenesis process, also called angio-miRNA and only few have been described till date. Anti-miRNA are miRNA-221 and miRNA-222 which block the angiogenesis process by their regulatory effect on stem cell factor receptor c-kit.[11] Sabatel et al[12] found miRNA-21 as negative regulator of angiogenesis, which act by targeting RHoB expression in endothelial cells. Apart from these, miRNA 17-992 and miRNA 17/20 have been integrated as negative regulator of angiogenesis. MiR-126 is a negative regulator of VEGF-A and promotes cell growth in oral cancer cells. Decreased miRNA-126 expression was associated with the induction of tumor

Table 1: Antiangiogenic drugs in cancer therapy

Sl. no.	*Drug*	*Description*
1	Bevacizumab	Recombinant anti-VEGF-A monoclonal antibody
2	Vandetanib	TKI: VEGFR-2 and EGFR
3	Sunitinib	TKI: VEGFR-1, 2, and 3, PDGFR-a and -b, stem cell factor receptor and fms-like tyrosine kinase 3
4	Sorafenib	TKI: VEGFR, PDGFR, stem cell factor receptor, B-Raf, C-Raf, fms-like tyrosine kinase 3
5	Motesanib	TKI: VEGFR, PDGFR, stem cell factor receptor
6	Linifanib	TKI: VEGFR, PDGFR

TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet derived growth factor receptor

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angiogenesis and lymphangiogenesis, tumor progression, nodal metastasis, and poor prognosis in the OSCC cases.[13] A recent study identified another set of miRNAs (miR-17 and miR-20a) as key regulators of the transcription of pro-angiogenic genes in tumor-associated macrophages via directly targeting hypoxia-induced factor-2a. The autocrine activity of interleukin-6 on tumor-associated macrophages plays an important role in this process.[14] We recommend that one should not disregard the importance of angio-miRNAs in carcinogenesis process which can modulate tumor angiogenesis process. Thus, they are highly potential targets for antiangiogenic therapy alone or in combination with other agents described in Table 1.

Human papilloma virus (HPV) 16 has been detected in 70% of oropharyngeal cancers. Human papilloma virus effectively modulates various events in carcinogenesis process and hence warrants special considerations in the development of therapeutic strategies.[15] It has been reported in the literature that HPV-16 E6 positive cells express high levels of VEGF. E6 oncoprotein upregulates the promoter activity of VEGF in a P53 independent manner, thus suggesting direct stimulation of VEGF gene.[16] Moreover, PI3K/Akt signaling pathway and c-Jun are involved in HPV-16 oncoprotein-induced hypoxia-induced factor-1a, VEGF, and interleukin-8 expression and *in vitro* angiogenesis.[17] Moreover, HPV-16 oncoprotein promotes hypoxia-induced factor-1a protein stability possibly through enhancing the interaction with c-Jun, thus making a contribution to angiogenesis in cancer cells.[17] With regard to this discussion, we believe that HPV-associated OSCC could respond differently to anti-angiogenic therapy. Hence, in future it is very important to consider "HPV-associated OSCC" as a separate entity while studying antiangiogenic therapy.

Interaction of miRNA with HPV-16 E6 and E7 is a widely recognized phenomenon.[18] Interestingly, recent studies on different cancer cell lines reported that HPV-16 E6 oncoprotein regulates the expression of miR-23a, miR-26a, and miR-34a and E7 regulates the expression of miR-17-92, miR-15b/16-2, and miR-106b-25.[19] In OSCC, Lajer CB et al[20] reported perturbations of 21 miRs by HPV infection with most significant in miRNA-127-3p and miRNA-363. From the perspective of such studies, it becomes imperative to conceive the probable association or interactions of angio-miRNA with HPV oncoproteins (E6 and E7). We believe that such interaction would have profound effect on fate of antiangiogenic therapy and future studies are needed in this direction to accomplish successful antiangiogenic therapy.

In vitro, *in vivo*, and clinical studies showed that stress-related process could impact pathways implicated in cancer-relevant biological processes.[21,22] It is well known that stress response pathways are associated with activation of pro-angiogenic cytokines (VEGF, IL6) and angiogenesis promoting molecules, such as signal transducer and activator of transcription factor-3. Stress-mediated stimulation of non-epinephrine can activate STAT-3 independent of IL-6, leading to its downstream effect on angiogenesis.[23] A recent study on head and neck cancer by Fang et al revealed greater VEGF expression in poorer psychosocial functioning patients. When examined by HPV status, the association between psychosocial functioning and VEGF remained significant among the patients who were HPV negative, but not among those patients who were HPV positive.[24] Thus, we believe that psychological intervention in OSCC patients could modulate the tumor angiogenesis and might act synergistically or additively with anti-angiogenic targeted therapy mentioned in Table 1.

Recently, a phenomenon called cellular cannibalism has been identified in OSCC, which is related to nutritional supply to the cancer cells.[25-27] The nutrition is mainly received from the blood vessels that grow surrounding the tumor and its impairment is associated with the development of cannibalistic phenotype in cancer cells. Hence, it would be interesting to see how OSCC showing increased cannibalistic activity responds to the antiangiogenic therapy.

About 98% of human genes are transcribed into non-coding RNA which is known by the name of "junk DNA." Unlike its name, it has been proved that junk DNA can have some functional activities. This non-coding RNA plays a role in stopping the malignant transformation of the normal cells. The prospects of junk DNA in oral cancer research have already been put forward.[28] The area that is still to explore is the association of it with angiogenesis.

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