Brief Communication

"Is it time for personalised medicine for Ameloblastoma?": A hypothesis

Bhaskar Narayan[1], Somesh Kumar[2], Priya Kumar[1], Aadithya B. Urs[1]

[1]Department of Oral and Maxillofacial Pathology and Microbiology, Maulana Azad Institute of Dental Sciences, [2]Department of Pediatrics, Maulana Azad Medical College, New Delhi, Delhi, India

Abstract Ameloblastoma is a benign odontogenic tumor that is locally destructive. The most common treatment option is surgery, which often results in disfigurement of the face. $BRAF^{V600E}$ is the common gene mutation associated with its pathogenesis. Therefore, this paper hypothesizes the use of targeted drug therapy against this mutated gene.

Keywords: Ameloblastoma, $BRAF^{V600E}$, targeted medicine

Address for correspondence: Dr. Priya Kumar, Department of Oral and Maxillofacial Pathology and Microbiology, Maulana Azad Institute of Dental Sciences, BSZ Marg, New Delhi - 110 002, Delhi, India.
E-mail: drpri_kumar@yahoo.com
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BACKGROUND

Ameloblastoma is one of the most commonly encountered odontogenic tumors in the Indian subcontinent. It is a benign tumor but is locally aggressive, necessitating surgical intervention, which may result in facial disfigurement, leading to physical and mental issues for the patient.[1] A consensus has been reached that mutation in the B-raf proto-oncogene serine/threonine kinase (BRAF) gene is the most frequently encountered alteration in the signaling pathways.[2] BRAF protein is involved in a wide array of cell mechanisms that include metabolism and proliferation. Numerous mutations of the BRAF gene have been identified in various tumors (malignant melanoma, colorectal cancer, and non-small cell lung cancers), with the missense mutation at 600 residues being the most frequent, where valine is replaced by glutamine (V600E). This results in the constitutive activation of the mitogen/extracellular-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK) signaling pathways, resulting in the proliferation and survival of tumor cells[3] [Figure 1].

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Main text

BRAF protein is made up of 766 amino acids and is divided into three major domains. The active state of the BRAF protein indicates that the DGF (Asp, Phe, Gly) motif has moved out of the pocket to facilitate the binding of ATP with the protein. The phosphorylation of the substrate takes place after ATP binds to the N-lobe and the substrate protein binds to the C-lobe. Therefore, the majority of the BRAF inhibitors are designed to bind with this hinge residue and hinder with the ATP binding.[4]

Vemurafenib, an inhibitor of the BRAF enzyme, has a biochemical affinity to selectively bind to the ATP binding site of mutated $BRAF^{V600E}$ and decrease signaling through the MAPK pathway. This leads to reduced transcription

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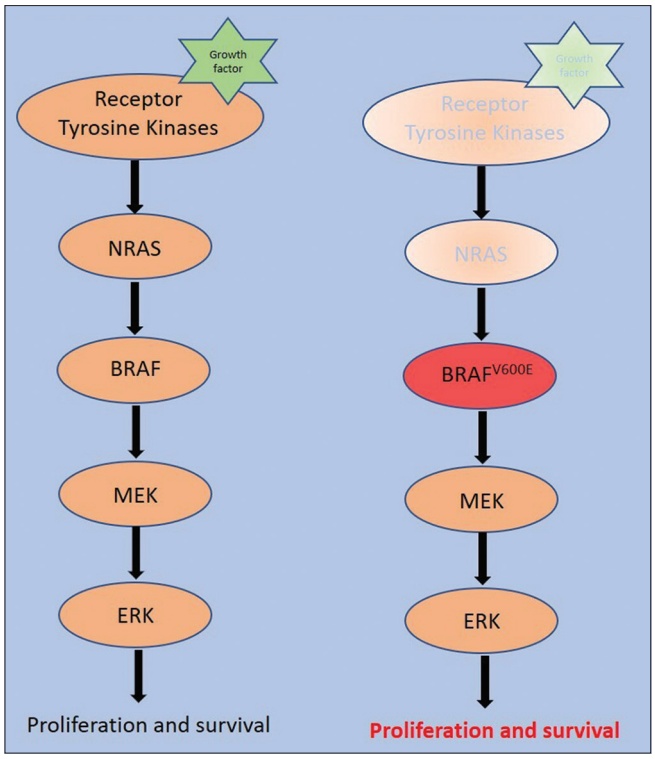

Figure 1: Growth factors bind receptor tyrosine kinases on the surface of the cell to stimulate proliferation and survival through the BRAF/MAPK/ERK pathway in normal cell vs. constitutive activation of BRAF in the absence of growth factors noted in $BRAF^{V600E}$ mutated cell lines, leading to overactivation of the signaling pathway

by inhibiting ERK phosphorylation, thereby checking cell proliferation and survival, and inducing G1 cell-cycle arrest and apoptosis in BRAF mutant tumor cells. This low molecular weight molecule is being used effectively in the treatment of malignant melanoma. Dabrafenib, another BRAF inhibitor, works on the same principle. A shortcoming of these two drugs is their ineffectiveness against wild type BRAF cells. Encorafenib, on the other hand, apart from targeting the $BRAF^{V600E}$, is found to be effective against the wild type mutation. It has been found that administration of these drugs inhibits tumor growth and, at higher doses, induces tumor regression in malignant melanoma cases.[5]

Also, the standard drug regime, that is, a combination of BRAF inhibitor with MEK inhibitor, is an advisable treatment option in BRAF mutated melanoma. The dual MAPK pathway inhibition prevents increased downstream signaling and, in turn, renders a more durable and potent inhibition of the ERK-related proliferation and apoptosis of cells.

These inhibitors are also known to cause immunomodulation, which reverses the immunosuppression in the tumor microenvironment of BRAF mutant tumors and turns them back into immunologically hot tumors. Hence, BRAF + MEK inhibitors cumulate immune response in the tumor microenvironment.[5]

CONCLUSION

We hypothesize the *in vitro* use of the same drug regime, that is, a combination of BRAF inhibitors with MEK inhibitors in the BRAF mutated ameloblastoma cell lines as they may limit the growth of tumor and thus decrease the need for disfiguring surgical procedures.

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Conflicts of interest
There are no conflicts of interest.

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