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Targeting mTOR in Head and Neck Cancer—Response

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We thank Masterson and colleagues for the kind and insightful comments, and for highlighting our team's efforts aimed at translating the emerging information of the head and neck cancer (HNSCC) oncogenome into new precision therapeutic options for this disease (1).

A striking finding from the deep sequencing of the HNSCC genomic landscape is the remarkable multiplicity and diversity of genetic alterations in this malignancy (2). This makes the search for actionable cancer-driving molecular events daunting. However, while the specific molecules altered in each individual tumor may be distinct, they all participate in only few network alterations, including those regulated by the *TP53, FAT1, NOTCH1, CASP8*, and *CDKN2A* ($p16^{INK4A}$) genes, and PI3K mutations (3). Among them, *PIK3CA*, encoding the PI3Kα catalytic subunit, is the most commonly mutated oncogene in HNSCC (2). We agree that these genomic studies have limitations, specifically for human papillomavirus (HPV)-associated oropharyngeal carcinomas due to their reduced number of cases in The Cancer Genome Atlas (TCGA; ref. 2). Hence, we agree that large scale deep sequencing genomic studies currently in progress may help refine the repertoire of targetable molecular pathways in HNSCC.

In this context, new bioinformatics tools may also help perform a network-based computational analysis of genomics and epigenetic alterations, rather than focusing solely on perturbations caused by single gene changes. Specifically, analysis of TCGA data from 428 HPV^- and 76 HP^+ HNSCC samples support that *PIK3CA* is the highest mutated cancer driving gene (16.8% in HPV^- and 25% in HPV^+ cases). However, these mutations are not sufficient to account for the widespread activation of the PI3K/mTOR pathway in HNSCC (>80% cases; ref. 4). For example, DNA gene copy-number gain of *PIK3CA* encoding the PI3Kα catalytic subunit, occur frequently in HNSCC (20.1% and 27.6%, in HPV^- and HPV^+ cases, respectively). Other PI3K isoforms (*PIK3CB, PIK3CD*, and *PIK3CG*) and multiple PI3K regulatory subunits also display mutations and copy-number

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gains (0.5%–11%). Low frequency of HNSCC cases also have mutations in *AKT2, mTOR*, or its regulatory subunits, *RICTOR* and *RAPTOR*.

Remarkably, a network-based analysis of the HNSCC oncogenome revealed that a high percentage of lesions also exhibit loss of at least one copy of a candidate PI3K/mTOR pathway tumor suppressor gene, *PTEN* (26%–34%), *TSC1* (13%–5%), *TSC2* (14%–12%), *STK11* (36%–17%), and *EIF4EBP1* (36%–9%; in each case, HPV^- and HPV^+ cases, respectively), and that HPV^+ cases are enriched for *PTEN* mutations (6.6%; ref. 5). This remarkable convergence of pathway-specific genomic alterations together with other epigenetic and posttranslational changes that are not reflected by these genomic analyses, including EGFR overexpression, may result in the persistent activation of the PI3K/AKT/mTOR pathway in most HNSCC lesions. This may in turn expose a cancer vulnerability that can be exploited therapeutically.

In this regard, building on the encouraging results from our recent clinical trial (1), we can expect that the ongoing large scale cancer sequencing efforts combined with computational and experimental approaches may soon reveal genetic alterations sensitizing to PI3K/mTOR-targeting agents, thus providing a novel network-based precision therapy strategy for HNSCC prevention and treatment.

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