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Commentary

Aurora kinases shed light on resistance to EGFR inhibition in head and neck cancer

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Despite technological improvements in cancer diagnosis and treatment, the 5-year survival rate of head and neck squamous cell carcinoma (HNSCC) patients remains largely stagnant [1]. Recently, immunotherapy has been FDA approved for use in this indication, resulting in a modest increase in overall survival and highlighting the need for additional therapeutics [1]. Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, regulates cancer cell survival, proliferation, and differentiation and is found frequently increased in cancer cells including HNSCC [2]. Although EGFR is often activated by mutation in diseases such as lung adenocarcinoma, in HNSCC overexpression of the wild-type receptor is often observed and presumed to be the basis of its hyperactivity [2,3]. Currently, cetuximab, a monoclonal antibody targeting EGFR, is the only targeted therapy available for the treatment of HNSCC [3]. This agent has limited utility with low response rates and rapid disease progression, highlighting challenges of both de novo and acquired resistance. The identification of biomarkers for efficacy have been a challenge and there is no correlation between EGFR expression and cetuximab response [4]. Several trials of small molecule inhibitors of EGFR have been trialed in HNSCC with limited success [2].

In this article of *EbioMedicine*, Joo-leng and colleagues [5] examined acquired resistance to gefitinib, an EGFR-tyrosine kinase inhibitor (TKI) in multiple EGFR wild-type HNSCC cell lines. Gefitinib resistant cells did not harbor any obvious genetic mutations that drive resistance (e.g. EGFR T790M), but rather overexpressed genes related to epithelial to mesenchymal transition (EMT) and genes that are repressed by the tumor microenvironment (TME). Although another reported driver of EGFR TKI resistance, AXL, was overexpressed and activation by phosphorylation was observed, AXL inhibition using siRNA or a selective AXL inhibitor (BGB324) could not re-sensitize the resistant cells to gefitinib. These results are unlike what

has been previously reported in non-small cell lung cancer (NSCLC) [6]. To identify a therapeutic target in these otherwise TKI resistant cells, a drug screening platform was established using more than 600 anti-cancer drugs and kinase inhibitors. Gefitinib-resistant cells were sensitive to microtubule inhibitors and cell cycle inhibitors including aurora kinase inhibitors (AKIs). Indeed, increased aurora kinase phosphorylation was observed in gefitinib-resistant cells which did not harbor amplification or overexpression of *AURKA* or *AURKB*. Activation of aurora kinases after EGFR inhibition was also previously seen in cetuximab-resistant HNSCC [7] and EGFR-TKI resistant NSCLC [8,9]. Gefitinib-resistant cells were commonly more sensitive to non-specific AKIs (TAK-901) than aurora kinase A specific inhibitors (MK-5108 and MLN8054). However, it is difficult to discern specific roles for AURKA or AURKB based on inhibitors that commonly inhibit both kinases at higher concentrations, and potential compensatory regulation between them [10]. Knockdown of either AURKA or AURKB resulted in increased apoptosis in resistant cells, suggesting that either paralog is required for resistance. Inhibition of aurora kinases did not alter EGFR downstream signaling molecules such as ERK and AKT. However, the effect of aurora kinase inhibition in decreased cell viability is possibly linked to activation of the pro-apoptotic BH3-only protein BIM [8], and apoptosis was further confirmed by caspase-3 activation in both gefitinib-resistant cell line and mouse xenograft model.

In this issue Joo-leng et al. describe a non-genetic molecular mechanism of gefitinib resistance in HNSCC that is associated with a dependence on aurora kinases. Their results raise a broader question of the specificity of signaling from AURKA or AURKB related to drug resistance. Because of their structural similarity, most inhibitors are not truly specific for one kinase over the other at the doses required to see significant antitumor activity in cells. Further complexity arises from recent data suggesting that inhibition of aurora B/C may counter the effects of aurora kinase A inhibition [10]. Next generation inhibitors such as a new ultra-specific inhibitor LY3295668 from Eli Lilly which has over 1000-fold specificity for AURKA over AURKB may help address questions of unique signaling from each kinase [10]. Lastly, these data highlight an emerging theme of cancer targets functioning in mitosis in the context of EGFR inhibition in HNSCC and NSCLC [7−9]. It remains unclear why EGFR oncogene inhibition results in a specific vulnerability in this phase of the cell cycle and the functional role for EGFR in supporting mitotic progression remains opaque since mitogen signaling is thought to be primarily active during interphase and silenced during mitosis. Given the broad role of

Aurora kinases in resistance to various EGFR inhibitors in different disease types, further work will be necessary to better understand this resistance mechanism and leverage it to develop inhibitors that can improve patient outcomes.

Contributors

D.K. and S.B. both performed literature search and wrote this manuscript.

Declaration of Competing Interest

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References

[1] Horton JD, Knochelmann HM, Day TA, Paulos CM, Neskey DM. Immune evasion by head and neck cancer: foundations for combination therapy. Trends Cancer 2019;5(4):208–32.

[2] Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001;37(Suppl 4):S9–15.

[3] Alsahafi E, Begg K, Amelio I, et al. Clinical update on head and neck cancer: molecular biology and ongoing challenges. Cell Death Dis 2019;10(8):540.

[4] Mehra R, Cohen RB, Burtness BA. The role of cetuximab for the treatment of squamous cell carcinoma of the head and neck. Clin Adv Hematol Oncol 2008;6(10):742–50.

[5] Low JL, Lau D, Zhang X, et al. A chemical genetic screen identifies Aurora kinases as a therapeutic target in EGFR T790M negative, gefitinib-resistant head and neck squamous cell carcinoma (HNSCC). EBioMedicine 2021;64.

[6] Zhang Z, Lee JC, Lin L, et al. Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. Nat Genet 2012;44(8):852–60.

[7] Boeckx C, Op de Beeck K, Wouters A, et al. Overcoming cetuximab resistance in HNSCC: the role of AURKB and DUSP proteins. Cancer Lett 2014;354(2):365–77.

[8] Shah KN, Bhatt R, Rotow J, et al. Aurora kinase A drives the evolution of resistance to third-generation EGFR inhibitors in lung cancer. Nat Med 2019;25(1):111–8.

[9] Bertran-Alamillo J, Cattan V, Schoumacher M, et al. AURKB as a target in non-small cell lung cancer with acquired resistance to anti-EGFR therapy. Nat Commun 2019;10(1):1812.

[10] Du J, Yan L, Torres R, et al. Aurora A-selective inhibitor LY3295668 leads to dominant mitotic arrest, apoptosis in cancer cells, and shows potent preclinical antitumor efficacy. Mol Cancer Ther 2019;18(12):2207–19.