Editorial

Stressing the need to overcome EGFR tyrosine kinase inhibitor resistance

Leila Toulabi, Bríd M. Ryan

Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Correspondence to: Bríd M. Ryan. Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20850, USA. Email: ryanb@mail.nih.gov.

Provenance: This is an invited Editorial commissioned by Section Editor Hengrui Liang (Nanshan Clinical Medicine School, Guangzhou Medical University, Guangzhou, China).

Comment on: Nilsson MB, Sun H, Diao L, *et al.* Stress hormones promote EGFR inhibitor resistance in NSCLC: Implications for combinations with beta-blockers. Sci Transl Med 2017;9(415).

Submitted Feb 02, 2018. Accepted for publication Mar 06, 2018.

doi: 10.21037/tlcr.2018.03.05

View this article at: http://dx.doi.org/10.21037/tlcr.2018.03.05

Lung cancer remains the leading cause of cancer-related mortality (1). This is partly due to the late stage at which lung cancer is diagnosed—more than 80% of lung cancers are diagnosed with either regional or distant metastasis (1). However, it is also partly because many patients' tumors are ultimately refractory to therapy. The genomic revolution has empowered a detailed understanding of cancer's genetic milieu and the identification of targetable gene alterations. In essence, these discoveries have revolutionized the management of many tumors, including lung cancer.

The epidermal growth factor receptor (*EGFR*) gene was identified in 1977 (2). The EGFR protein is a transmembrane glycoprotein member of the protein kinase superfamily, its key ligand is the growth factor EGF. Binding induces receptor dimerization and tyrosine autophosphorylation, which drives cell proliferation. Seventeen years after its discovery, the first tyrosine kinase inhibitor (TKI) targeting EGFR was described in 1994 (3). In unselected lung cancer patients, the response rates were approximately 10%, with increased responses observed in women, never smokers, and patients of Asian descent (4,5). These observations were subsequently linked to the finding that *EGFR* mutations are mostly observed in adenocarcinomas among never smokers. In 2003, gefitinib received FDA approval as a second-line agent for the for the treatment of unselected lung cancer patients. A year later, erlotinib received similar approval. However, Haber and colleagues made the key observation that activating *EGFR* mutations—such as exon 19 deletions and L858R—governed responsiveness to gefitinib (6), a key finding that led the FDA to approve erlotinib and afatinib as a first-line treatment for *EGFR*-mutant NSCLC in 2011. Nowadays, screening for *EGFR* mutations is mandatory prior to selecting a first-line treatment for stage IV lung adenocarcinoma.

In most cases, treatment with these agents extends patient survival but does not reduce patient mortality: eventually resistance emerges. Several mechanisms have been identified, key among them *EGFR* T790M mutations (7). Indeed, third-line *EGFR* TKIs have been developed—such as osimertinib—that are effective in T790M-positive patients (8). However, in nearly 50% of cases, resistance is T790M-independent.

In a recent issue of *Science Translational Medicine* (9), Nilsson and colleagues present evidence that elevated levels of stress hormones, particularly norepinephrine (NE), may contribute to EGFR TKI resistance in T790M-negative lung cancer. The authors had previously observed NE and epinephrine (E) receptors on the surface of ovarian cancer cells and seen that simulation of these receptors led to an increase in interleukin-6 (IL-6). Coupled with the previous observation that IL-6 is a mediator of T790M-independent EGFR TKI resistance (10), the authors pursued the hypothesis that stress hormones can mediate resistance to EGFR-specific TKIs.

In a series of *in vitro* and *in vivo* models, the authors

found that the stress hormone NE increased IL-6 through binding to β-adrenergic receptors, inactivating the tumor suppressor LKB1 and increasing p-CREB-dependent signaling. Expression of three adrenergic receptor genes were found on lung cancer cells, though expression of the β2-adrenergic receptor was highest. Subsequent experiments using β2 and β1 receptor antagonists demonstrated that the effect of stress hormones on IL-6 was dependent on the β2 subtype. This finding was somewhat surprising, as NE is known to mainly signal through alpha adrenergic receptors. E has strong selectivity for the β2-adrenergic receptor and while E was shown to increase IL-6 (in comparable magnitude to NE), most of the experiments in the study focused on NE.

In mice transplanted with EGFR-mutant cancer cells, chronic stress—modeled using established restraint methods—increased tumor IL-6 expression and accelerated tumor growth. Treatment of mice with erlotinib resulted in tumor regression. Mice treated with erlotinib and a β-adrenergic agonist became resistant. However, the addition of a β-blocker to erlotinib and the β-adrenergic agonist prevented the development of resistance.

Interestingly, the effect of NE on IL-6 induction was most pronounced in cells with activating *EGFR* mutations, with little to no effect seen in *EGFR* wild-type cells. No difference in β2-adrenergic receptor gene expression was observed between mutant and wild-type cells. However, a physical interaction between the β2-adrenergic receptor and mutant EGFR was demonstrated, suggesting that there is cooperative signaling between these two proteins. Notably, such an interaction was not observed with wild-type EGFR, a hint perhaps, for why these findings are restricted to *EGFR*-mutant cancers. Also, the effects were not seen in non-malignant human bronchial epithelial cells.

Do these findings have relevance for human patients? For several years, epidemiological literature has supported a relationship between psychosocial stress and cancer survival (11). The use of beta-blockers has also been linked with lung cancer survival, though there have been some inconsistencies across studies (12-17). In light of Nilsson *et al.'s* findings, it is possible that some of the incongruent findings could be related to the genetic subtype of the tumors studied. Moreover, first generation beta-blockers targeting both the β1 and β2 adrenergic receptors, while second generation drugs mainly target just β1 (this subtype is primarily expressed on the myocardium) which could have also confounded conclusions. Evidence from experimental studies suggests that psychological stress can drive metastasis (18-24). For example, when mice bearing human tumors were confined or isolated from other mice—conditions that increase stress—their tumors were more likely to metastasize. The authors attempted to address the question of human relevance using retrospective analyses of clinical trial data. For example, using data from the ZEST trial, they found that high pre-treatment plasma levels of circulating IL-6 were associated with a poor response to EGFR inhibitors. Furthermore, in the BATTLE trial patients reporting incidental use of beta-blockers had decreased IL-6, further evidence that the *in vitro* and xenograft models may have human relevance. Perhaps most interestingly, a retrospective analysis of data from the LUX-LUNG 3 study, a phase III clinical trial comparing afatinib or cisplatin plus pemetrexed in patients with *EGFR* mutations, found data consistent with their preclinical findings: Specifically, that incidental use of a beta-blocker could delay the onset of EGFR TKI resistance. The researchers acknowledge that these analyses were limited in their retrospective nature. While the findings are consistent with their preclinical data and support the hypothesis that β-blockers may prevent EGFR TKI resistance, a prospective randomized study is needed to potentially change the standard of care.

Such prospective studies would determine whether the use of beta-blockers delay or prevent resistance to EGFR TKIs. The analysis of the LUX-LUNG 3 data suggested that resistance is delayed. Therefore, additional work may be needed to identify new strategies to exit out of what seems to a cyclical issue of emergent TKI resistance. The authors' data suggest that there may be two possible strategies. For example, in addition to blocking the β2-adrenergic receptor, the authors found that using an IL-6 inhibitor, such as siltuximab, could prevent erlotinib resistance, even in the presence of a β-adrenergic agonist. Thus, this could be an alternative approach to overcome potential resistance.

The use of beta-blockers in the context of the study by Nilsson and colleagues was aimed at blocking the physiological effects of stress on cancer cells via a pharmacological mechanism. Alternatively, is it possible that stress management techniques, such as mindfulness or exercise might achieve similar results? Mindfulness, a form of meditation, has been shown to reduce the physiologic markers of stress such cortisol, CRP, blood pressure and heart rate (25). However, it remains to be seen whether stress management techniques could produce the same benefit as the beta-blockers in this study and would need to

be studied in a prospective fashion.

The work by Nilsson and colleagues demonstrates that the stress hormone NE may act directly on tumor cells and promote resistance to EGFR TKIs, evidence that suggests beta blockers, which are well-tolerated and inexpensive, may improve response to EGFR targeting TKIs. Such drug repurposing, i.e., the use of a drug that is an already-approved compound for a new indication, is an attractive prospect, as it can be faster, cheaper and less risky than developing a new drug from scratch. If beta blockers can delay or prevent resistance to EGFR TKI inhibitors, patients could be given a well-tolerated, cost-effective drug. The field optimistically awaits the prospective trials that could ultimately translate the implications of this work to patient care.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
2. Das M, Miyakawa T, Fox CF, et al. Specific radiolabeling of a cell surface receptor for epidermal growth factor. Proc Natl Acad Sci U S A 1977;74:2790-4.
3. Ward WH, Cook PN, Slater AM, et al. Epidermal growth factor receptor tyrosine kinase. Investigation of catalytic mechanism, structure-based searching and discovery of a potent inhibitor. Biochem Pharmacol 1994;48:659-66.
4. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol 2003;21:2237-46.
5. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149-58.
6. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
7. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005;352:786-92.
8. Walter AO, Sjin RT, Haringsma HJ, et al. Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. Cancer Discov 2013;3:1404-15.
9. Nilsson MB, Sun H, Diao L, et al. Stress hormones promote EGFR inhibitor resistance in NSCLC: Implications for combinations with beta-blockers. Sci Transl Med 2017;9(415).
10. Yao Z, Fenoglio S, Gao DC, et al. TGF-beta IL-6 axis mediates selective and adaptive mechanisms of resistance to molecular targeted therapy in lung cancer. Proc Natl Acad Sci U S A 2010;107:15535-40.
11. Batty GD, Russ TC, Stamatakis E, et al. Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. BMJ 2017;356:j108.
12. Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol 2008;5:466-75.
13. Weberpals J, Jansen L, Haefeli WE, et al. Pre- and post-diagnostic beta-blocker use and lung cancer survival: A population-based cohort study. Sci Rep 2017;7:2911.
14. Weberpals J, Jansen L, van Herk-Sukel MP, et al. Immortal time bias in pharmacoepidemiological studies on cancer patient survival: empirical illustration for beta-blocker use in four cancers with different prognosis. Eur J Epidemiol 2017;32:1019-31.
15. Wang H, Liao Z, Zhuang Y, et al. Incidental receipt of cardiac medications and survival outcomes among patients with stage III non-small-cell lung cancer after definitive radiotherapy. Clin Lung Cancer 2015;16:128-36.
16. Cata JP, Villarreal J, Keerty D, et al. Perioperative beta-blocker use and survival in lung cancer patients. J Clin Anesth 2014;26:106-17.
17. Shah SM, Carey IM, Owen CG, et al. Does beta-adrenoceptor blocker therapy improve cancer survival? Findings from a population-based retrospective cohort study. Br J Clin Pharmacol 2011;72:157-61.
18. Williams JB, Pang D, Delgado B, et al. A model of gene-environment interaction reveals altered mammary gland gene expression and increased tumor growth following social isolation. Cancer Prev Res (Phila) 2009;2:850-61.
19. Moreno-Smith M, Lutgendorf SK, Sood AK. Impact of stress on cancer metastasis. Future Oncol 2010;6:1863-81.

20. Lutgendorf SK, Sood AK, Antoni MH. Host factors and cancer progression: biobehavioral signaling pathways and interventions. J Clin Oncol 2010;28:4094-9.
21. Lutgendorf SK, Lamkin DM, Jennings NB, et al. Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma. Clin Cancer Res 2008;14:6839-46.
22. Lutgendorf SK, DeGeest K, Sung CY, et al. Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. Brain Behav Immun 2009;23:176-83.
23. Lutgendorf SK, DeGeest K, Dahmoush L, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. Brain Behav Immun 2011;25:250-5.
24. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nat Rev Cancer 2006;6:240-8.
25. Pascoe MC, Thompson DR, Jenkins ZM, et al. Mindfulness mediates the physiological markers of stress: Systematic review and meta-analysis. J Psychiatr Res 2017;95:156-78.

Cite this article as: Toulabi L, Ryan BM. Stressing the need to overcome EGFR tyrosine kinase inhibitor resistance. Transl Lung Cancer Res 2018;7(Suppl 2):S123-S126. doi: 10.21037/tlcr.2018.03.05

