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Research Article

PTEN Status Alters the Molecular Route to Resistance to BRAF Inhibitor in Melanoma

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Although targeted treatment by BRAF inhibitors (BRAFi) achieved a remarkable clinical response for patients with BRAF mutation, the strength of efficacy is short and limited by acquired drug resistance [1]. Recent studies identified many mechanisms of acquired resistance to BRAFi, such as mutations in NRAS or MEK1 and overexpression of COT, EGFR, PDGFRβ, IGF1R or MET, lead the reactivation of MAPK pathway and drive the cell proliferation, suggesting that co-targeting this hyperactivated survival pathway by combination inhibitors might gain the maximum clinical benefits for melanoma patients [2]. Based on these findings, FDA approved the combination of dabrafenib (BRAFi) with trametinib (MEK inhibitor) or vemurafenib (BRAFi) with cobimetinib (MEK inhibitor) to inhibit the MAPK signaling pathway in 2014 and 2015 more effectively. Indeed, the dual inhibitors of MEK and mutant BRAF kinases have shown a higher overall survival rate and exciting results in initial tumor response in clinical [2]. Moreover, this combinational treatment can prevent or delays the acquired resistance. However, the benefit of the combination did not last too long due to anew therapy resistance, which continues to obstacle the clinical applications. Novel strategies and molecular mechanism are therefore needed to improve the precision and efficiency of targeted therapy for resistant melanoma.

Malignant melanoma is recently characterized as widely mutated in multiple genes. These multiple genetic alternations have reasonably thought not only to cause the poor response to current treatments but also may alter the molecular route to resistance to the targeted therapy. Understanding the alternative molecular route that causes resistance would improve the clinical application of targeted therapies through developing innovative strategies to make a better patient selection and to improve the precision and durability of responses for the personalized combination therapies. As well known, the tumor suppressor PTEN is another most common mutated or lost gene in melanoma. Inactivation of PTEN by mutation occurs in up to 35% of melanomas. Interestingly, the PTEN mutation is always with a concurrent BRAF mutation. PTEN effectively antagonizes the PI3K and AKT, thereby inhibiting cell proliferation and promoting apoptosis. The loss of PTEN is reported to contribute to intrinsic resistance to BRAF inhibitor via the suppression of BIM-mediated apoptosis [3].

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Clinically, the BRAF mutant patients with PTEN loss/mutation showed a trend for shorter median PFS on BRAF inhibitor therapy compared with wild-type PTEN patients in melanoma [4]. Although recent studies indicate that melanoma cell lines with inactivated PTEN can be growth arrested by BRAF and MEK inhibitors, they are resistant to apoptosis induction [5]. Together, these reports support that PTEN inactivation identifies a distinct clinically significant subset of melanomas, implying that PTEN status may affect the molecular mechanism of late acquired resistance to BRAFi. In our recent study, we reasonably hypothesized that inactivated PTEN alters downstream pathways to contribute to acquired BRAFi resistance in melanoma [6].

To study the role of PTEN in resistance to BRAFi, we selected BRAF mutant melanoma cells with/without wild-type PTEN and established BRAF inhibitor-resistant melanoma models. The results from comparative analysis of the resistant melanoma models have shown that MAPK signaling pathway was hyper-reactivated in all BRAFi resistant melanoma cells as a major pathway of acquired BRAFi resistance independent of PTEN status, but the PI3K/AKT signaling pathway was only hyperactivated in BRAFi resistant melanoma cells with wildtype PTEN. Interestingly, neither treatment with MEK inhibitor (MEKi) alone nor combination with BRAFi could inhibit the growth of resistant melanoma cells with wildtype PTEN, whereas an AKT inhibitor (AKTi) significantly inhibited their growth. However, both MEKi and AKTi combination with BRAFi or triple combinations (MEKi+AKTi+BRAFi) could inhibit proliferation of the resistant melanoma cells with impaired PTEN. The data suggested that the oncogene addiction resulted in both hyperactivated ERK and AKT pathways associated with the resistance to BRAF inhibitor in melanoma with wild-type PTEN. The melanoma cells with impaired PTEN and hyperactivated AKT require only ERK resistance mechanism to BRAF inhibitor (Figure 1).

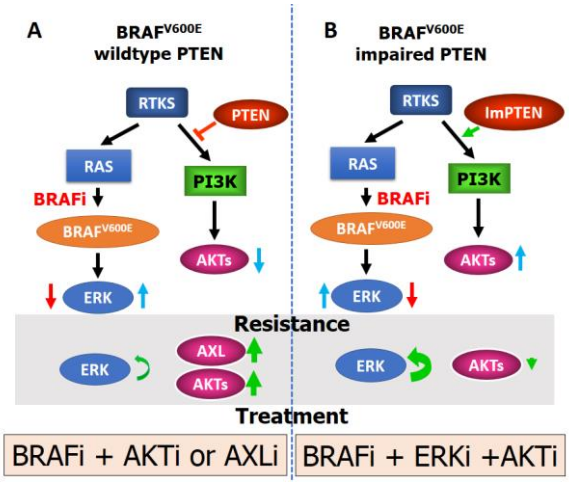

Figure 1: Model of the BRAF inhibitor (BRAFi) resistant melanoma with different PTEN status. **(A)** In BRAF mutant melanoma with wildtype PTEN, both ERK and AKT resistance mechanisms may be involved in melanoma cells with wildtype PTEN resistance to BRAFi. AXL is a critical upstream effector of AKT. The combination therapy of BRAFi and AKT inhibitor (AKTi) or AXL inhibitor (AXLi) induces tumor apoptosis and is a benefit for BRAF mutant melanoma patients with wildtype PTEN. **(B)** The melanoma cells with impaired PTEN (ImPTEN) and hyperactivated AKT require only ERK resistance mechanism to BRAFi. The combination therapy of BRAFi and MEK inhibitor (MEKi) or AKTi could be a benefit for BRAF mutant melanoma patients with impaired PTEN.

Also, we discovered that phosphorylated AXL was significantly increased in BRAFi-resistant melanoma with wildtype PTEN but not in with impair PTEN using protein array [6]. Earlier work had already suggested that AXL could promote tumor aggressiveness and confer to resistance to many MAPK inhibitors in various types of tumors including melanoma [7, 8]. Indeed, blocking AXL by shRNA and/or small molecular inhibitor could rescue the sensitivity of resistant melanoma cells with wildtype PTEN to BRAFi and inhibit their growth *in vitro* and *in vivo*. In contrast, overexpression of AXL reduced the sensitivity of BRAFi in melanoma with wildtype PTEN [6].

Notably, we found that activated AXL played a significant role in the regulation of acquired BRAFi resistance in melanoma cells with wildtype PTEN through mechanistically activating AKT, but not in melanoma with impaired PTEN. Our data demonstrated that AXL/AKT axis mediated-resistance to BRAFi depends on PTEN status, suggesting AXL is a new prognostic marker and therapeutic target for BRAFi resistance in $BRAF^{V600E}$ mutant melanoma with wildtype PTEN. Our findings have significant implications for personalized medicine strategies and therapies for acquired BRAFi resistance in melanoma with different PTEN status.

Conflicts of interest

No conflicts of interest were disclosed.

References

1. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC et al. (2012) Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 366: 707-714. [Crossref]
2. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF et al. (2012) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 367: 1694-1703. [Crossref]
3. Paraiso KH, Xiang Y, Rebecca VW, Abel EV, Chen YA et al. (2011) PTEN loss confers BRAF inhibitor resistance to melanoma cells through the suppression of BIM expression. *Cancer Res* 71: 2750-2760. [Crossref]
4. Nathanson KL, Martin AM, Wubbenhorst B, Greshock J, Letrero R et al. (2013) Tumor genetic analyses of patients with metastatic melanoma treated with the BRAF inhibitor dabrafenib (GSK2118436). *Clin Cancer Res* 19: 4868-4878. [Crossref]
5. Deng W, Gopal YN, Scott A, Chen G, Woodman SE et al. (2012) Role and therapeutic potential of PI3K-mTOR signaling in de novo resistance to BRAF inhibition. *Pigment Cell Melanoma Res* 25: 248-258. [Crossref]
6. Zuo Q, Liu J, Huang L, Qin Y, Hawley T et al. (2018) AXL/AKT axis mediated-resistance to BRAF inhibitor depends on PTEN status in melanoma. *Oncogene* 37: 3275-3289. [Crossref]
7. Brand TM, Iida M, Stein AP, Corrigan KL, Braverman CM et al. (2014) AXL mediates resistance to cetuximab therapy. *Cancer Res* 74: 5152-5164. [Crossref]

8. Zhang Z, Lee JC, Lin L, Olivas V, Au V et al. (2012) Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. *Nat Genet* 44: 852-860. [Crossref]