Commentary

Repurposing an HIV drug to improve efficacy of targeted therapy in melanoma

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Targeted mitogen-activated protein kinase inhibitor (MAPKi) therapies have had limited efficacy in patients with v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) -mutant, unresectable or metastatic melanomas and tumor relapse is almost inevitable (1). There has been a great deal of studies dissecting heterogeneous molecular mechanisms of acquired resistance to mutant *BRAF*-targeted therapies. For example, up-regulation of mitochondrial biogenesis and altered tumor bioenergetics (2), increased phosphorylation of protein kinase B (*AKT*) (3), and selection for subpopulations expressing epidermal growth factor receptor (*EGFR*) (4) are mechanisms responsible for acquired resistance. Some approaches to overcome acquired drug resistance are combining MAPKi with immune checkpoint blockade inhibitor targeting programmed cell death protein 1 (PD-1) (5), targeting both the MAPK and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT pathway (6), and targeting mitochondrial biogenesis through inhibition of tumor necrosis factor receptor-associated protein 1 (TRAP1) (2). However, much work needs to be done in investigating and therapeutically preventing the emergence of the initial intrinsic resistance to MAPKi.

Several studies have implicated microphthalmia-associated transcription factor (*MITF*) as a key driver of intrinsic drug resistance. Drug-sensitivity to MAPKi is correlated with expression and activity of *MITF* and inversely correlates with nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*) and AXL receptor tyrosine kinase (*AXL*) expression (7). A *MITF*-low/*AXL*-high/drug-resistance phenotype is common in *BRAF*- and neuroblastoma RAS viral oncogene homolog (NRAS)-mutant melanoma cell lines (8). Smith and colleagues built upon these and other *MITF* studies as a driver of intrinsic drug resistance, which is reversible and non-mutational (9). *MITF* and paired box 3 (PAX3) are concurrently up-regulated as an adaptive response to MAPKi and ultimately drive initial intrinsic resistance. This result was consistent with *PAX3's* known function as a transcriptional regulator of *MITF* (10). The authors hypothesized that inhibiting *MITF* and *PAX3* would improve MAPKi efficacy and identified nelfinavir mesylate, an HIV-1 protease inhibitor, as a potent inhibitor of those genes in a drug screen (*Figure 1*).

Nelfinavir inhibited *MITF* and *PAX3* expression by up-regulating the mothers against decapentaplegic homolog 2/mothers against decapentaplegic homolog 4/Ski (SMAD2/SMAD4/SKI) repressor complex. Nelfinavir also increased phosphorylated SMAD2 and SKI repressor bound to PAX3. Suppression of *MITF* and *PAX3* by nelfinavir improved the efficacy of MAPKi by inhibiting tumor growth to a greater degree. Ectopic overexpression of *MITF* and *PAX3* rescued the tumor's survival ability to MAPKi. Mechanistically, mitogen-activated protein kinase kinase (MEK) suppressed PAX3 through SKI, which stimulated SMAD2 to repress the *PAX3* promoter.

Nelfinavir sensitized not only *BRAF*- but also *NRAS*-mutant melanoma cells to MAPKi. Interestingly, even in melanoma cells without up-regulated *MITF*, the improved sensitivity to MAPKi through nelfinavir was still effective. This combination therapy is especially relevant for patients with *NRAS*-mutant melanomas, who have markedly worse clinical prognosis and no FDA approved targeted therapies (11). The

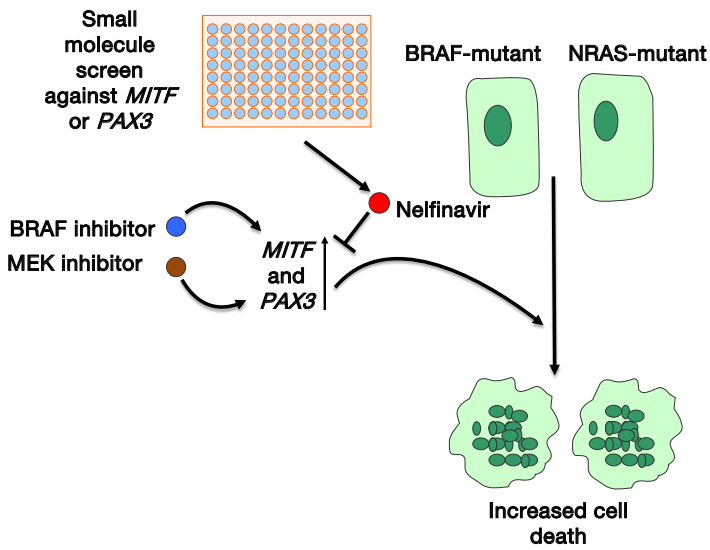

Figure 1 Improving efficacy of MAPKi with nelfinavir. MAPKi such as BRAF and MEK inhibitors lead to increased *MITF* and *PAX3* expression. A small molecule screen against *MITF* and *PAX3* identified nelfinavir as the most potent inhibitor. Nelfinavir in combination with MAPKi leads to increased cell death and could improve clinical response to MAPKi therapies.

increase in expression of *MITF* in *NRAS*-mutant melanoma cells upon MEK inhibition has been shown previously (12). Thus, Nelfinavir may also be effective in combination use with the MEK1/2 inhibitor, MEK162, to treat NRAS-mutant melanomas (13).

MITF also directly regulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1α*) and drives oxidative phosphorylation (14). Suppression of *MITF* with nelfinivir may synergize with MAPKi and inhibit aberrant oxidative metabolism, which is a significant MAPKi-acquired resistance mechanism. Altered tumor metabolism and bioenergetics are important considerations when assessing the full effects of new combinatorial therapies.

Drug repositioning, or repurposing an existing drug for a new usage, has become increasingly recognized and can provide a new source of potent inhibitors in melanoma therapy. Another example of drug repositioning is riluzole, used in treatment of amyotropic lateral sclerosis, which can inhibit cell proliferation of metabotropic glutamate receptor 1 (GRM1)-expressing melanoma cells (15). Using existing drug libraries previously unexplored for anti-tumor activity can bear new fruits of discovery.

Taken together, Smith and colleagues identify a clinically relevant combinatorial therapy through drug repositioning that could improve initial response to targeted MAPKi therapy. *MITF* repression has been linked to increased cell invasion and metastasis (16). Thus, there needs to be further studies to fully examine the nelfinavir and MAPKi combination. Nonetheless, this study is an important step in discovering new personalizable combinatorial treatments that could improve response to targeted therapies and perhaps even immunotherapies.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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