Cell Death

Major Finding: LPR8 was identified as a factor contributing to ferroptosis resistance in multiple tumor types.

Concept: LPR8 loss decreases selenium levels, in turn reducing GPX4 through ribosome stalling and translation inhibition.

Impact: These findings expose a therapeutic vulnerability that can sensitize cancer cells to ferroptosis.

LOSS OF LPR8 REDUCES GPX4 LEVELS, RESULTING IN FERROPTOSIS SENSITIVITY

Ferroptosis, a regulated form of necrotic cell death, can be prevented by the activity of GPX4, a glutathione-dependent peroxidase and selenoprotein that previous studies have indicated can induce ferroptosis when inhibited. However, cancer cells show variability in their sensitivity to ferroptosis, and the mechanisms that cells use to prevent ferroptosis and regulate GPX4 remain undefined. Thus, Li and colleagues used a chemical–genetic screen and identified the lipoprotein receptor LRP8 as a regulator of ferroptosis resistance across a broad range of cancer types. A robust interaction was observed between LRP8 and glutathione metabolism and selenium-related factors such as GPX4 and selenocysteine (SEC) synthesis, notable as LRP8 serves as a receptor for the SEC-rich protein selenoprotein P (SEPP1), which when broken down releases selenium. Knockout of LRP8 decreases selenium levels by approximately 60%, with addition of selenite (Se), a form of selenium taken up independently of LRP8, rescuing this reduction and ferroptosis sensitivity. Moreover, LRP8 knockout significantly reduced GPX4 levels as well as levels of some other selenoproteins, which could also be rescued by Se addition but not by ferroptosis inhibitors, with this loss being reversed only upon reexpression of LRP8 mutants that are able to bind to SEPP1. Additionally, normal epithelial cells lines did not demonstrate these alterations to GPX4 expression, suggesting a cancer cell–specific phenotype. Furthermore, counter to the prevailing selenoprotein regulatory hierarchy, GPX4 was indicated to be one of the initial proteins reduced after selenium depletion, with studies investigating the role of GPX4 in mediating LRP8 knockout ferroptosis sensitivity revealing that limited selenium due to LRP8 knockout reduces GPX4 and subsequent ferroptosis. Mechanistically, the loss of GPX4 was induced by abrogated translation caused by ribosome stalling and premature translation termination leading to proteasomal clearance. In summary, these findings indicate LRP8 as a factor in cancer cell ferroptosis resistance, which mediates its effects through selenium and GPX4 translation, and suggest the targeting of selenoproteins to sensitize cancer cells to ferroptosis. ■

Li Z, Ferguson L, Deol KK, Roberts MA, Magtanong L, Hendricks JM, et al. Ribosome stalling during selenoprotein translation exposes a ferroptosis vulnerability. Nat Chem Biol 2022;18:751–61.

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Drug Resistance

Major Finding: Androgen receptor (AR) expression increases upon BRAF/MEK inhibitor treatment, promoting resistance.

Concept: BRAF/MEK inhibitors plus pharmacologic inhibition of AR improved tumor control in male and female mice.

Impact: AR inhibition combined with BRAF/MEK-targeted therapies could improve clinical outcomes in melanoma.

RESISTANCE TO BRAF/MEK INHIBITION IN MELANOMA IS MEDIATED BY THE ANDROGEN RECEPTOR

BRAF/MEK inhibitors have improved outcomes in melanoma, but resistance is common. The male sex has been associated with worse outcomes in melanoma, and in hormone-responsive cancers, like prostate cancer, the androgen receptor (AR) has been indicated to interact with the MAPK signaling pathway. However, the relationship between AR and BRAF/MEK inhibitor resistance in melanoma has not yet been elucidated. To investigate the role of AR in mediating BRAF/MEK inhibitor resistance in melanoma, Vellano, White, Andrews, Chelvanambi, Witt, and colleagues studied over 600 patients with metastatic melanoma treated with neoadjuvant BRAF/MEK-targeted therapies and showed reduced tumor burden, a higher rate of major pathologic response (MPR), as well as improved relapse-free and progression-free survival in female patients as compared to male patients. Evaluation of AR expression in pretreatment and posttreatment patient samples revealed significantly higher AR expression in male posttreatment samples, while female patients showed a similar trend that did not achieve statistical significance. Moreover, higher AR expression was observed in patients who did not achieve an MPR on BRAF/MEK inhibitors, while those who did showed no significant changes to AR expression. Preclinical models were used to validate these results as well as identify strategies to improve response and survival outcomes and showed that male mice have impaired tumor control as compared to female mice, and pharmacologic inhibition of AR in combination with BRAF/MEK-targeted therapies in mouse models of melanoma demonstrated improved tumor control and reduced tumor size in both male and female mice that could be abrogated by testosterone treatment. Furthermore, AR expression as well as expression of androgen-responsive genes were also found to be higher in mice treated with both testosterone and BRAF/MEK therapies versus BRAF/MEK therapies alone. Overall, these results reveal the role of AR in mediating resistance to BRAF/MEK-targeted therapies in melanoma and suggest that combining AR inhibition with BRAF/MEK inhibitors could lead to improved clinical response. ■

Vellano CP, White MG, Andrews MC, Chelvanambi M, Witt RG, Daniele JR, et al. Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy. Nature 2022;606:797–803.

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