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Editorial

Fasting-mimicking diet potentiates anti-tumor effects of CDK4/6 inhibitors against breast cancer by suppressing NRAS- and IGF1-mediated mTORC1 signaling

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ABSTRACT

Fasting-mimicking diet (FMD) cycles, defined as 3–5 day periods of a calorie-restricted, low-protein, low-carbohydrate, and high-fat diet, have emerged as a dietary approach to delay cancer initiation and progression in both autograft and xenograft mouse models and as a safe and feasible approach to decrease risk factors for cancer and other age-related pathologies in humans. A substantial number of pre-clinical studies focused on various tumor types have shown that fasting/FMDs can potentiate the efficacy of various standard-of-care cancer therapies but also modulate the immune system to promote a T cell-dependent attack of tumor cells. Importantly, combining drug treatment with fasting/FMDs can overcome acquired drug resistance which frequently emerges and reduces long-term treatment benefits. However, the mechanisms by which the FMD reverts resistance to CDK4/6i remain poorly understood. Here, Li and colleagues provide evidence that FMD cycles act as a wild card to reduce the activity of a signaling network that includes IGF-1, RAS, AKT, and mTOR-S6K to delay cancer progression and reverse the acquisition of drug resistance.

These findings expand the mechanistic understanding of the FMD-mediated increase in drug efficacy and provide further evidence to support trials combining hormone therapy, CDK4/6 inhibitors, and FMD in breast cancer treatment. These new results on FMD cycles add an optimistic outlook to extend the efficacy of standard-of-care drugs that eventually become ineffective because of acquired resistance.

Fasting-mimicking diet (FMD) cycles, defined as 3–5 day periods of a calorie-restricted, low-protein, low-carbohydrate, and high-fat diet, have emerged as a dietary approach to delay cancer initiation and progression in both autograft and xenograft mouse models and as a safe and feasible approach to decrease risk factors for cancer and other age-related pathologies in humans (Vernieri et al., 2024). Clinical trials are also beginning to support the effect of FMD cycles in potentiating immune response and the efficacy of cancer drugs, particularly against breast cancer (Vernieri et al., 2022; Vernieri et al., 2024) while reducing treatment-related adverse events and improving patient quality of life. Normal cells down-regulate the IGF-1, RAS, AKT, and mTOR-S6K signaling network and other proto-oncogene pathways and limit cellular proliferation in response to the fasting/FMD-induced changes in nutrient availability while activating cellular resilience to protect against the toxic side effects caused by cancer treatments, including chemotherapy, hormone therapy, kinase inhibitors, and immunotherapy. Malignant cells however are characterized by dysregulated cellular proliferation driven in part by oncogenic mutations that constitutively activate pro-growth pathways, incl. RAS, AKT, and mTOR-S6K signaling, that render tumor cells largely unresponsive to the anti-growth signals caused by fasting/FMDs (Lee et al., 2010). A substantial number of pre-clinical studies focused on various tumor types (incl. breast, melanoma, prostate, colorectal, etc.) have shown that fasting/FMDs can potentiate the efficacy of various standard-of-care cancer therapies but also modulate the immune system to promote a T cell-dependent attack of tumor cells (Caffa et al., 2015; Cortellino et al., 2022; Di Biase et al., 2016; Lee et al., 2010), thereby indicating a broad therapeutic potential. Importantly, combining drug treatment with fasting/FMDs can overcome acquired drug resistance which frequently emerges and reduces long-term treatment benefits (Caffa et al., 2020). However, the mechanisms by which the FMD reverts resistance to CDK4/6i remain poorly understood.

In this issue of *Drug Resistance Updates*, Li et al. are exploring the molecular mediators of the effects of FMD cycles in overcoming acquired drug resistance to the CDK4/6i abemaciclib using transcriptomic analysis of two CDK4/6i-sensitive and CDK4/6i-resistant breast cancer cell lines (Li et al., 2024). Their gene set enrichment analysis suggested that, compared to parental cells, the two drug-resistant cell lines increased AKT1 and mTOR signaling and pointed to mTORC1 as the main driver for acquired CDK4/6i resistance. In fact, mTORC1 inhibitors (everolimus) *in vivo* and *in vitro* and knockdown of the positive mTORC1 regulators RAPTOR and RHEB confirmed this hypothesis. In line with previous studies that demonstrate that the FMD can inhibit the mTOR-S6K signaling cascade and reverse acquired drug resistance (Caffa et al., 2020), the authors hypothesized that FMD cycles may reverse the resistance of specific breast cancer cell lines to therapy by down-regulating mTORC1 signaling. Indeed, abemaciclib alone does not significantly inhibit tumor growth of two CDK4/6i-resistant breast cancer cell lines, and the FMD alone only induces a moderate growth inhibition, whereas the combination of abemaciclib and FMD

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significantly reduces tumor growth of both drug-resistant cell lines, indicating that CDK4/6 signaling acts as an escape pathway activated by these drug-resistant cancer cells to survive during fasting conditions (Li et al., 2024). Reduced levels of the circulating growth factor IGF1, a positive regulator of the mTOR-S6K signaling axis, was previously shown to act as a key mediator of the fasting/FMD-induced killing of cancer cells, and the administration of IGF1 during the fasting/FMD cycle is sufficient to reverse these toxic effects (Lee et al., 2012; Lee et al., 2010). Li et al. show that IGF1 treatment results in the reversal of the FMD-induced cell growth inhibition in SUM159 and MDA-MB-231 breast cancer cells via decreased levels of phosphorylated S6. Additional gene set enrichment analysis points to NRAS signaling down-regulation for combining abemaciclib and FMD vs. abemaciclib alone in MDA-MB-231 cells. Together, these studies identify RAS family members and IGF1 as upstream regulators of mTORC1, making the network, including IGF1, RAS, AKT, and mTOR-S6K, a target to reverse acquired CDK4/6i resistance. Interestingly, cell models of the aggressive triple-negative breast cancer (TNBC) subtype have been reported to have various degrees of sensitivity to CDK4/6 inhibitors. Still, their effect is potentiated by FMD cycles in combination with the PI3K inhibitor pictilisib (Salvadori et al., 2021). Here Li et al. confirm that the combined treatment with abemaciclib and FMD inhibits TNBC tumor growth *in vitro* and *in vivo (*Li et al., 2024*)*. These studies warrant clinical trials to test whether FMD cycles can potentiate the efficacy of CDK4/6 inhibitors, possibly in combination with PI3K inhibitors, to reverse drug resistance, or to characterize potential side effects/patient compliance issues of this combination therapy.

In conclusion, Li and colleagues provide evidence that FMD cycles act as a wild card to reduce the activity of a signaling network that includes IGF-1, RAS, AKT, and mTOR-S6K to delay cancer progression and reverse the acquisition of drug resistance. These findings expand the mechanistic understanding of the FMD-mediated increase in drug efficacy and provide further evidence to support trials combining hormone therapy, CDK4/6 inhibitors, and FMD in breast cancer treatment (Vernieri et al., 2024). Combined with the high degree of patient compliance and favorable safety profile in various clinical trials (Vernieri et al., 2024), these new results on FMD cycles also add an optimistic outlook to extend the efficacy of standard-of-care drugs that eventually become ineffective because of acquired resistance.

CRediT authorship contribution statement

Valter D. Longo: Writing – original draft, Writing – review & editing. **Sebastian Brandhorst:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

V.D.L. has equity interest in and serves as an advisor of L-Nutra, a company making medical food. V.D.L. and S.B. have filed patents related to the FMD at the University of Southern California. The University of Southern California has licensed intellectual property to L-Nutra; as part of this license agreement, the University has the potential to receive royalty payments from L-Nutra.

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