

## INSIGHTS

# Stress relief of chemo illness

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New studies (Tang et al. 2024. *J. Exp. Med.* <https://doi.org/10.1084/jem.20231395>) describe a liver stress pathway that is activated by certain chemotherapeutic drugs, which in turn induces a peptide hormone which partially mediates the lower food intake and body weight loss during chemotherapy treatment.

Preclinical studies have identified a liver-brain hormone axis partially responsible for unwanted anorexia during chemotherapy, potentially paving the way for new therapeutic options. Chemotherapy is a cornerstone of cancer treatment, but some chemotherapies have unwanted side effects such as nausea and reduced food intake (Gupta et al., 2021). This is particularly deleterious, as cancer can drive involuntary weight loss and tissue wasting on its own, in a condition known as cancer cachexia, which is responsible for up to 30% of cancer deaths (Schiessel and Baracos, 2018). These side effects reduce efficacy of cancer treatments by reducing treatment windows—patients need a level of physical robustness to withstand the rigors of chemotherapy (Schiessel and Baracos, 2018). In their new paper (Tang et al., 2024), a team of scientists from Hangzhou, China, led by Ying Wu and Bo Shan, show that a class of chemotherapeutic drugs selectively activates a branch of the unfolded protein response exclusively in the liver. In particular, a common “endoplasmic reticulum” and “unfolded protein response” (UPR) signature was detected when examining differential gene expression profiles from livers of mice treated with body weight loss-inducing chemotherapeutic drugs doxorubicin and cisplatin.

Given that there are three major pathways triggered during the UPR, namely PERK, IRE1 $\alpha$ , and ATF6 (Hetz et al., 2020), it was important to determine which of these

were involved. Indeed, an IRE1 $\alpha$ -XBP1s (but not PERK nor ATF6) pathway was shown to be induced (Tang et al., 2024). Importantly, this profiling was done using high-throughput mRNA sequencing (mRNAseq) a day after administration of the drugs, which avoided confounding effects of substantial body weight loss. How, and precisely why, the liver IRE1 $\alpha$  arm of the UPR was activated by systemic administration of remains unclear, although it may be similar to a mechanism described for another toxin where direct binding to IRE1 $\alpha$  caused activation (Simpson et al., 2024). Nevertheless, hepatocyte-selective silencing of IRE1 $\alpha$  using a genetic model partially blocked the reduction in food intake and body weight with both doxorubicin and cisplatin. Importantly, this was confirmed in a tumor-bearing model. However, it should be noted that these effects were only partial, with an ~50% blunting of the reduction of food intake, and a very mild effect on the blunting of body weight loss, when compared to the vehicle control arm. One is then left wondering what other factors contributed to the reduced body weight and food intake with chemotherapeutic drug treatment. Conceivably, as also noted by the authors, the body weight reduction could result from other factors such as effects on digestible energy assimilation from the gastrointestinal tract as well as effects on energy expenditure relative to intake. Additionally, body fluid balance is a major



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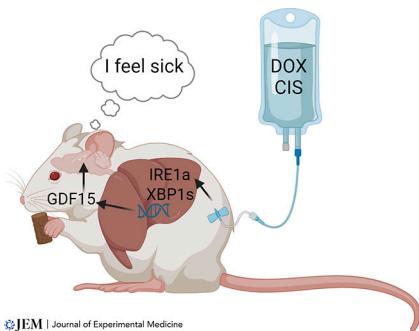
factor contributing to body weight, and tracking water intake as well urinary fluid and electrolyte loss would be insightful. A good place to start would be body composition analyses using magnetic resonance imaging or dual x-ray absorptiometry technologies. Future studies should clearly consider these aspects.

A highlight of the paper was use of a chemical inhibitor of IRE1 $\alpha$ , namely 4 $\mu$ 8C, in conjunction with chemotherapy to highlight the druggable nature of this target. 4 $\mu$ 8C inhibits the RNase activity of IRE1 $\alpha$  with low toxicity in cellular studies in vitro (Cross et al., 2012). Similar to the genetic studies, inhibition of IRE1 $\alpha$  using this compound partially blocked the reduced food intake and body weight observed with both doxorubicin and cisplatin treatment. This result should spur further preclinical trials examining inhibition of IRE1 $\alpha$  using drugs to block unwanted side effects from chemotherapies. Dosing (i.e., 3.3 mg/kg in

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Platinum-based chemotherapeutics doxorubicin (DOX) and cisplatin (CIS) activate the IRE1 $\alpha$  arm of the UPR in the liver, which in turn stimulates GDF15 secretion and sickness behaviors such as depressed food intake.

DMSO+Cremophor) of the 4 $\mu$ 8C was quite high, and whether this would be realistic in humans requires consideration. It should be noted that despite these appealing results, 4 $\mu$ 8C shows off-target effects (Sato et al., 2017) and can affect T cell responses (Kemp et al., 2013), which may also impact other therapies such as immunotherapies. In any case, there are several classes of IRE1 $\alpha$  inhibitors (Wiese et al., 2022) that could be explored. Indeed, IRE1 $\alpha$  inhibition might also have added benefits beyond attenuating anorexia, as hepatic IRE1 $\alpha$  activation can lead to inflammation and damage (Dasgupta et al., 2020).

So, how can induction of a liver-specific stress pathway lead to effects on food intake and body weight? Based on the knowledge that liver-derived peptide hormones can convey such effects downstream of stress signaling pathways, the authors reanalyzed their liver mRNAseq data for potential secreted factors, and uncovered Gdf15 is a commonly upregulated transcript (Tang et al., 2024). Elevation of plasma GDF15 was confirmed through serum peptide assays. Furthermore, this appears to be clinically relevant, as they could show that humans undergoing chemotherapy have substantially elevated blood GDF15 levels, which is in congruence with prior observations (Breen et al., 2020). Similar to the IRE1 $\alpha$  experiments, whole-body and liver-specific Gdf15 silencing partially blocked the reduced food intake and body weight seen with chemotherapy, and liver Gdf15 induction by chemo drugs was shown to require the IRE1 $\alpha$ -XBP1s pathway. These effects of GDF15 are robust in this setting, as they validate prior findings showing that

GDF15 blockade alleviates chemotherapy-induced anorexia and weight loss (Breen et al., 2020) and that other stressors such as nutritional stressors affect metabolic adaptations via a liver XBP1s-GDF15 axis (Zhang et al., 2018).

Since its discovery in 1997, multiple roles for GDF15 have been described across areas of metabolism, appetite, and cancer progression (Lockhart et al., 2020; Tsai et al., 2018) without a known receptor. In 2017, four papers published in the same month identified the orphan receptor glial cell-derived neurotrophic factor receptor  $\alpha$ -like (GFRAL) as the receptor for GDF15 (Lockhart et al., 2020; Tsai et al., 2018). They described the anatomical location of this receptor as being limited to the area postrema and nucleus tractus solitarius in the hindbrain (Lockhart et al., 2020; Tsai et al., 2018). For a small, discrete population of neurons to mediate the pleiotropic functions described for GDF15 is staggering, and points to an unrecognized contribution of the brain to a range of functions such as skeletal muscle metabolism and cancer progression. The current paper uses c-FOS protein immunoreactivity as a readout of GFRAL neuronal activity in an attempt to identify the role of hindbrain GFRAL neurons in the observed effects on body weight and appetite. However, this specific methodology is not sufficient to elucidate the dynamic regulation of these neurons in response to chemotherapy, and likely simply reflects the differing plasma concentrations of GDF15 at time of sacrifice, and over the previous 8 days of treatment. If hindbrain GFRAL is indeed the only target of circulating GDF15, this paper describes a hitherto unknown liver-brain axis critically important in control of appetite loss in response to noxious stimuli. The downstream targets of hindbrain GFRAL neurons include areas known to be involved in food aversion and nausea (Sabatini et al., 2021; Worth et al., 2020), but much work is still to be done to understand the neuronal circuits in which GFRAL neurons are embedded.

Importantly, the GDF15/GFRAL field has heavily utilized whole-body knockout mice on the understanding that GFRAL is selectively expressed in the hindbrain. This may turn out to be a limiting factor in the field, as no studies have yet reported whole-body GFRAL expression in (patho)physiological

states with chronically elevated GDF15, such as cancer, obesity, chronic inflammatory disease, aging, or pregnancy. Given therapeutic interventions targeting this system are currently being explored for obesity and cachexia, this is a question that needs to be addressed sooner rather than later.

The subjective feeling of sickness in rodents can be assessed using a battery of behavioral tests, including assessment of locomotor activity and conditioned aversion to a taste stimulus to assess nausea. GDF15 appears to be a key player in chemotherapy-induced fatigue (Chelette et al., 2023), and it seems likely the improvements in feeding in the current manuscript are due to decreased GDF15-mediated aversion and nausea caused by cisplatin and doxorubicin, but specific behavioral assays to detect this will add weight to the use of anti-IRE1 $\alpha$  agents as adjuncts to human chemotherapy treatment. In any case, the appetite loss and nausea experienced by people with lived experience of cancer is deeply debilitating, and better treatment options are desperately needed. This paper takes a small step toward filling this clinical therapy gap.

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