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An Antibody Attack against Body Wasting in Cancer

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Cachexia is a devastating, non-curable condition in many cancer patients that is marked by severe wasting of the muscle and fat tissue. Its prevention has been hampered by an insufficient knowledge of the underlying molecular mechanism(s) that lead to its pathogenesis. Suriben et al. (2020) now report the development and characterization of an antagonistic antibody for the previously identified GDF15-GFRAL axis that efficiently blocks tumor-induced body wasting in experimental animals.

Characterized by an uncontrollable, severe, and progressive loss or wasting of body mass, most prominently of adipose tissue and muscle, cachexia is an irreversible metabolic disorder that frequently accompanies chronic diseases and is critically linked to poor prognosis in cancer, with up to 80% of fatalities, depending on cancer type (Baracos et al., 2018). Conventional nutritional support to counteract anorexia or antibody therapies against inflammatory cytokines have largely failed to elicit therapeutic responses. Despite recent advances in identifying cachexia mediators and underlying molecular principles, notably inflammation, proteolysis, and lipolysis, an efficient therapeutic approach to stop the body wasting is yet to be found. This suggests cachexia likely involves a complex interplay between various energy homeostatic pathways and multiple tissues (Rohm et al., 2019). In this context, the stress response-associated cytokine growth differentiation factor 15 (GDF15), a member of the TGFβ superfamily, has been shown to control energy homeostasis under various pathologic conditions including cancer (Tsai et al., 2018). Upon cellular stress, elevated levels of circulating GDF15 cause anorexia, and recombinant GDF15 is sufficient to induce weight loss in mice. The recently identified and highly localized GDF15 receptor GDNF receptor alpha-like (GFRAL) is expressed mainly in the area postrema and the nucleus tractus solitarius, areas of the hindbrain critically involved in appetite regulation. In this region, GFRAL signals through Ret proto-oncogene (RET) to induce activation of AKT, ERK1/2, and PLCγ (Figure 1) (Tsai et al., 2018). Suppression of food intake is one of the major consequences of GDF15-GFRAL signaling, but recent studies suggest it also elicits metabolic effects independent of feeding behavior (Luan et al., 2019). Accordingly, tumors overexpressing GDF15 induce anorexia and cachexia in mice, whereas genetic knockout of GDF15 or GFRAL causes obesity (Tsai et al., 2018). Importantly, GDF15 action seems to be limited to pathophysiological conditions so far. It is therefore not surprising that the GDF15-GFRAL axis is a promising target for cachexia research.

Anorexia is only one of many factors contributing to cachexia, and multiple energy-wasting or catabolic pathways are activated in response to the tumor. Notably, cachectic adipocytes display elevated lipolysis, which is in part mediated by an increased sympathetic tone. The importance of lipolysis for cachexia development is highlighted by studies in mice lacking the key lipases adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), which are protected from cancer cachexia (Das et al., 2011).

Starting from a hybridoma screening approach, Suriben et al. (2020) now report on the identification of a monoclonal antibody, 3P10, able to specifically inhibit GFRAL-RET signaling at picomolar concentrations, in a RET ligand-independent fashion. Interestingly, 3P10 did not prevent GDF15 binding to GFRAL but rather prevented the physical interaction between the GFRAL extracellular domain (ECD) and the RET ECD at the cell surface. Indeed, the 3P10-GFRAL ECD crystal structure revealed binding of 3P10 to the GFRAL D3, but not the GDF15-binding D2 domain. Of note, at atomic resolution 3P10 and RET used an identical interaction epitope (Arg294) on the GFRAL ECD that was found to be functionally relevant for GFRAL-RET downstream signaling *in vitro* and *in vivo*. In this respect, acute 3P10 injection abrogated GDF15-dependent neuronal activation in the brainstem, whereas chronic antibody administration accelerated high-fat-diet-induced body weight gain in wild-type mice, thereby overall mimicking the GFRAL knockout phenotype (Hsu et al., 2017; Mullican et al., 2017).

Intriguingly, the 3P10 antibody was able to both prevent and restore body weight loss in experimental animals carrying GDF15-expressing tumors with minimal, if any, effects on food intake, which was in stark contrast to the prototypical GDF15-driven body weight phenotype that mostly relies on reduced caloric intake. In fact, improved body weight maintenance even under restricted feeding conditions suggested that the 3P10-mediated body weight gain in tumor-bearing mice could not be explained by enhanced energy intake. Overall, the results point to an as-yet unknown food intake-independent mechanism of GDF15 action in systemic energy homeostasis.

In line with a reversal of tumor-enhanced lipid oxidation by 3P10, antibody-treated, tumor-carrying mice displayed major gene expression changes in adipose tissues. Interestingly, GDF15 triggered enhanced expression of

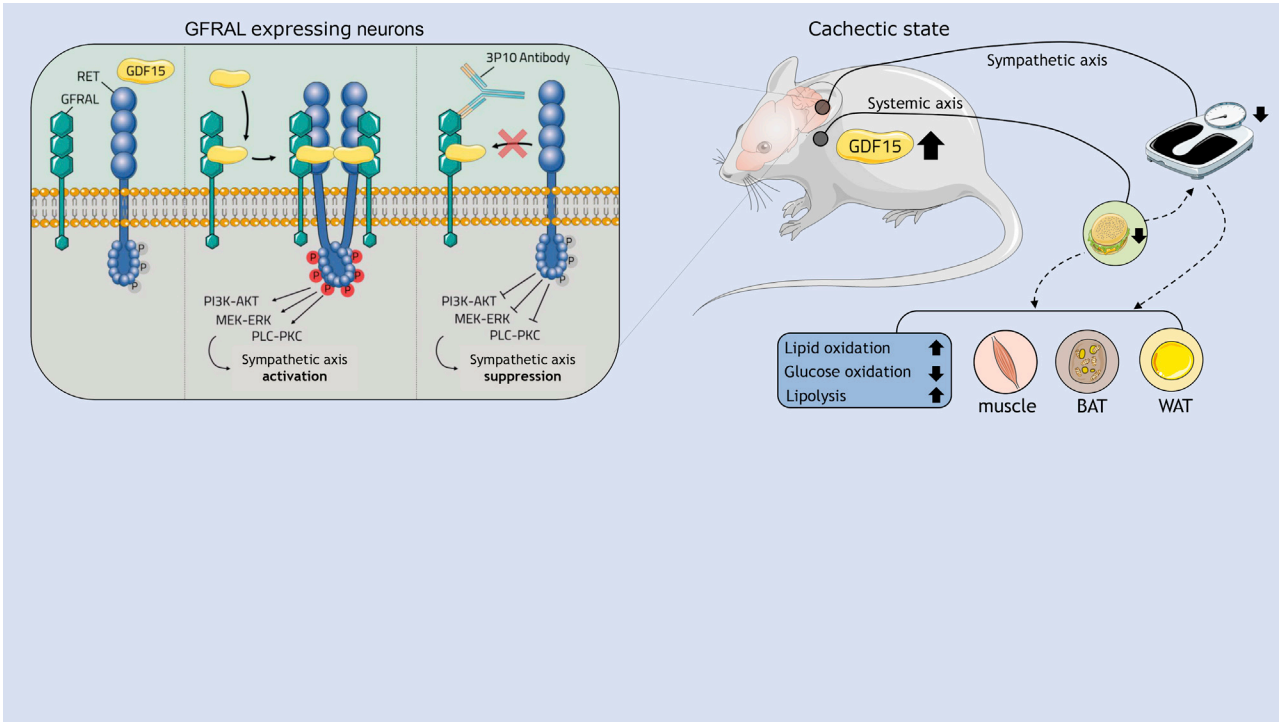

Figure 1. An Antibody Approach to Treat Cancer Cachexia

Left: GDF15 binding to GFRAL in neurons of the area postrema and the nucleus tractus solitarius promotes GFRAL-RET binding and subsequent activation of downstream signaling cascades. 3P10 antibody binding to GFRAL impairs RET binding. Right: elevated circulating GDF15 levels during cachexia act on systemic and sympathetic axes to suppress food intake and body mass, respectively, while affecting the muscle, BAT, and WAT. WAT, white adipose tissue; BAT, brown adipose tissue.

ATGL, which was dependent on GFRAL expression. Of note, in ATGL knockout mice GDF15 lost its impact on body weight, suggesting that ATGL-mediated lipolysis represents a key component of the GDF15-GFRAL regulatory axis in systemic body weight control. Finally, expanding the concept of GDF15-dependent peripheral circuits, pharmacological denervation of peripheral sympathetic neurons abrogated GDF15-triggered body weight loss while leaving its regulatory functions for food intake intact. These findings suggest that the GDF15-GFRAL pathway employs distinct central (food intake) and peripheral (lipid oxidation, lipolysis) pathways to control body weight, particularly under cancer cachectic conditions.

As cancer cachexia still represents an unmet clinical need, the identification of 3P10 as an antibody-based, potential therapeutic approach to tumor-induced body wasting holds great promise for the field, particularly since detailed crystal structures are now available for further pharmacological refinements in this context.

While the conceptual advance in GDF15 peripheral actions as developed by Suriben et al. (2020) is clearly in line with the notion that anorexia is only one component of the cachectic phenotype beyond substantial catabolic adaptations in the peripheral compartments, a number of unsolved questions remain.

In particular, how GDF15-mediated preservation of body mass is achieved without a major impact on food intake remains enigmatic and requires further elucidation of energy expenditure and metabolic efficacy. A thorough mechanistic study of GDF15 action in the context of cachexia will hopefully shed further light on its interaction with different metabolic tissues, known cachexia modulators such as inflammation, and the causality of directly or indirectly affected signaling pathways. In this regard, the regulatory principles of ATGL expression, in particular, and the contribution of sympathetic signaling to systemic GDF15 action require future attention. From a pharmacological perspective, it will be interesting to explore the antibody's impact on the peripheral and sympathetic GDF15 targets, and to test antibody efficacy in distinct tumor entities.

Despite the more widespread expression of GFRAL in human tissues compared to mice, which may hamper the specificity of this antibody approach and foster unwanted side effects (Mullican et al., 2017), the receptor and its antagonistic antibody provide a promising novel concept to treat cachexia in the clinic.

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