CLINICAL IMPLICATIONS OF BASIC RESEARCH

Cancer Cachexia and Fat–Muscle Physiology

Kenneth C.H. Fearon, M.D.

Cachexia affects the majority of patients with advanced cancer and is associated with a reduction in treatment tolerance, response to therapy, quality of life, and duration of survival. It is a multifactorial syndrome caused by a variable combination of reduced food intake and abnormal metabolism that results in negative balances of energy and protein. Cachexia is defined by an ongoing loss of skeletal-muscle mass[1] and leads to progressive functional impairment. Although appetite stimulants or nutritional support can help reverse the loss of fat, the reversal of muscle wasting is much more difficult and remains a challenge in patient care.

The loss of skeletal muscle in cachexia is the result of an imbalance between protein synthesis and degradation. Much recent work has focused on the ubiquitin–proteasome pathway, the regulation of satellite cells in skeletal muscle, and the importance of related receptors and signaling pathways that are probably influenced by tumor-induced systemic inflammation.[2] Similarly, the loss of adipose tissue results from an imbalance in lipogenesis and lipolysis, with enhanced lipolysis driven by neuroendocrine activation and tumor-related lipolytic factors, including proinflammatory cytokines and zinc-α_2-glycoprotein.[3]

The study of integrative physiology in obesity and diabetes has long emphasized the importance of chronic inflammation, increased adipocyte lipolysis, and increased levels of circulating free fatty acids in the adipose–muscle cross-talk that contributes to lipotoxicity and insulin resistance in muscle. Similarly, studies in exercise physiology have focused on the molecular cross-talk between adipose tissue and muscle that occurs through adipokines and myokines and on the role these molecules may play in chronic diseases. Although cachexia in patients with cancer is characterized by systemic inflammation, increased lipolysis, insulin resistance, and reduced physical activity, there has been little effort to manipulate the integrative physiology of adipose tissue and muscle tissue for therapeutic gain.

To this end, Das and colleagues[4] recently reported the results of experiments involving two mouse models in which the metabolic end of the cachexia–anorexia spectrum was investigated. In these mice, during the early and intermediate phases of tumor growth and cachexia, food intake remained normal while plasma levels of proinflammatory cytokines and zinc-α_2-glycoprotein rose. The investigators found that genetic ablation of adipose triglyceride lipase prevented the increase in lipolysis and the net mobilization of adipose tissue associated with tumor growth (Fig. 1). Unexpectedly, they also observed that skeletal-muscle mass was preserved and that activation of proteasomal-degradation and apoptotic pathways in muscle was averted. Ablation of hormone-sensitive lipase had similar but weaker effects. This study opens up the possibility that hitherto unrecognized, physiologically important cross-talk between adipose tissue and skeletal muscle exists in the context of cancer cachexia.

What is the translational relevance of these findings? Given the current epidemic of obesity in Western society in general and in patients with cancer in particular, the inhibition of fat loss is probably not a priority in itself. The key problem remains low muscle mass, with up to 50% of persons with advanced cancer having frank sarcopenia. Moreover, the shortest survival times among patients with advanced cancer may be among obese patients with sarcopenia.[5] In such patients, any muscle-preserving therapy that also increases fat mass might not be advantageous. It should also be considered that the metabolic response to cancer is heterogeneous, and a therapy that is tailored to a specific metabolic abnormality may require specific, individualized characterization of patients. Moreover, cachexia has a spectrum of phases (precachexia, cachexia, and refractory cachexia) and degrees

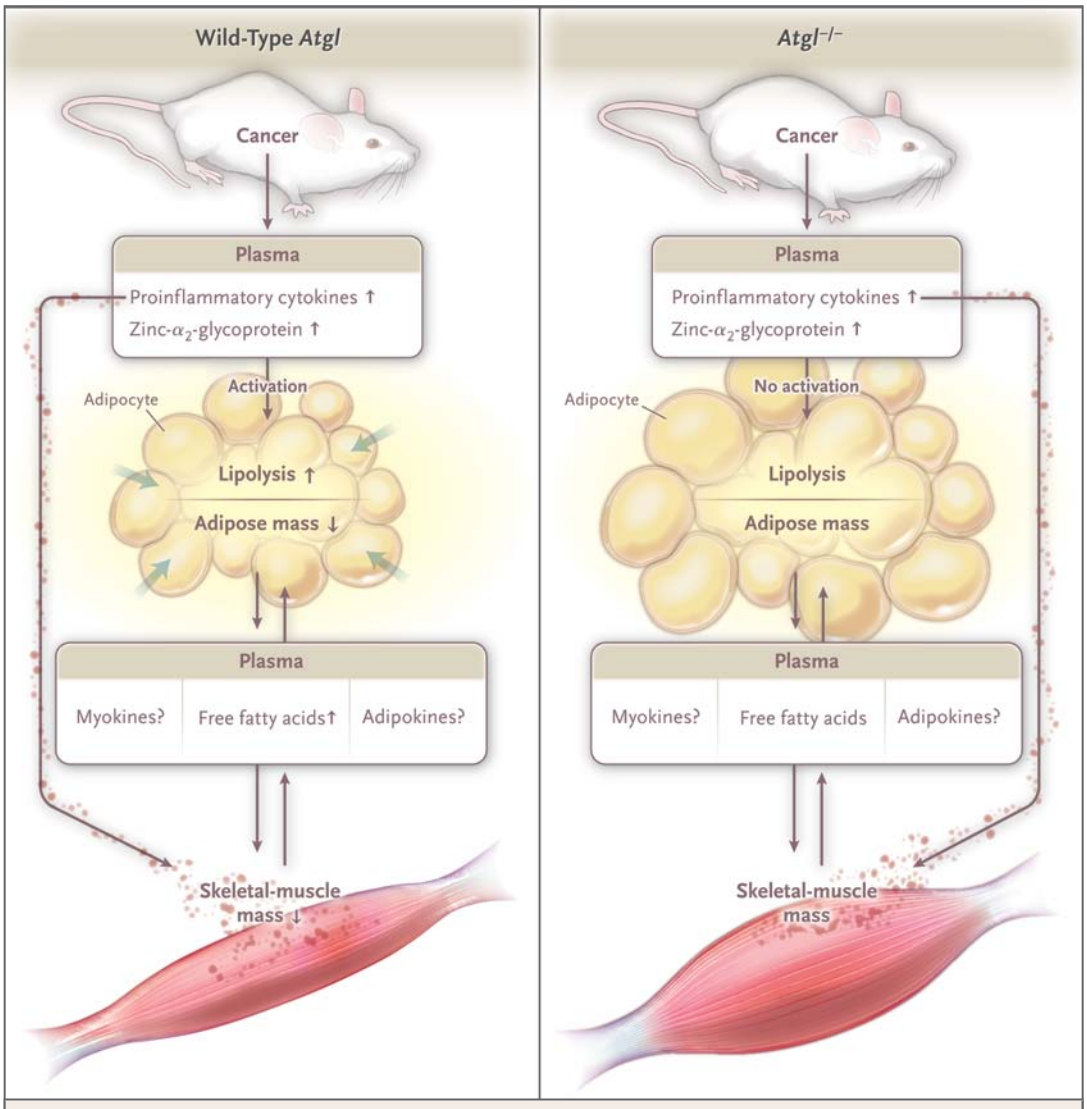

Figure 1. Model of Cachexia and Lipolysis in Tumor-Bearing Mice with Wild-Type *Atgl* or *Atgl*$^{-/-}$.

In tumor-bearing mice with the wild-type gene for adipose triglyceride lipase (*Atgl*, also known as *Pnpla2*), a variety of circulating mediators, including cytokines (tumor necrosis factor α and interleukin-6) and zinc-α_2-glycoprotein, activate Atgl, which triggers lipolysis, resulting in net mobilization of white adipose tissue and an increase in plasma levels of free fatty acids. Concomitantly, cachexia — the process of protein catabolism, apoptosis, and muscle atrophy — begins and may be modulated by cross-talk between muscle and adipose tissue mediated by free fatty acids or by various adipokines or myokines. In tumor-bearing mice in which the *Atgl*$^{-/-}$ gene has been ablated, the same pattern of mediator release fails to activate lipolysis, plasma levels of free fatty acids remain normal, and both white adipose tissue mass and skeletal-muscle mass are maintained. The mechanism through which skeletal-muscle mass is maintained in the presence of the systemic mediators is unknown but may involve muscle-adipose cross-talk through free fatty acids, myokines, or adipokines. Alternatively, the maintenance of skeletal-muscle mass may be a direct consequence of autonomous lipolysis in defective tissue.

of severity.[1] Das and colleagues tested the effect of ablation of lipolysis at the onset of tumor growth. Thus, their model does not address the scenario that frequently occurs in clinical practice, in which both cancer and cachexia are well established. Finally, patients generally receive systemic antineoplastic therapy until a late stage in their disease trajectory, and the interaction of this treatment with the development of cachexia (some treatments may induce muscle wasting)

is unknown. Taken together, these issues point to the importance of understanding the precise mechanism underlying the findings of Das and colleagues.

Traditionally, controlling the advance of cancer has been viewed as the best way to contain cachexia. However, symptom management alone can improve survival in patients with advanced cancer, and a multifaceted approach to the management of cachexia has already proved to be partially effective.[1] The growing understanding of the mechanisms underpinning cachexia has prompted an increasing number of studies, now in phase 1 or phase 2, that use highly specific, potent therapies targeted at either upstream mediators or downstream end-organ hypoanabolism and hypercatabolism. The study by Das and colleagues suggests that achieving a better understanding of the integrative physiology of this complex syndrome may yield yet further novel therapeutic approaches.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Clinical Surgery, School of Clinical Sciences and Community Health, University of Edinburgh, Royal Infirmary, Edinburgh.

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