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White Adipose Tissue Browning and Cancer Cachexia

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Cachexia or wasting syndrome is often seen in cancer patients. Over half of the patients suffer from this condition although the incidence varies from tumor types. Symptoms of cancer cachexia include progressive weight loss, anorexia, depletion of adipose tissues and loss of skeletal muscle mass. Treatment with nutrient supplements or appetite stimulants often fails to reverse these metabolic abnormalities. Thus far, the exact mechanism in which how cancer causes cachexia is poorly understood. One hypothesis is that tumors secrete factors to induce protein degradation in skeletal muscles and enhance lipolysis in adipocyte tissues. Concordantly, early studies have shown that animal models with tumor removal reverse these metabolic symptoms. Thus, there is a mounting interest of identifying these tumor-derived factors, which may aid the development of new therapeutic interventions. Recently, new findings have shed new light into this strenuous area in which parathyroid hormone related protein (PTHrP) [1] and Interlukin-6 (IL-6) [2] have been found to be inducer for cancer cachexia. Both factors have important biological functions for many well-known processes. For instance, PTHrP plays critical roles during fetal development and postnatal epithelial differentiation [3]. In Particular, PTHrP is an important factor to regulate cartilage and bone homeostasis [4]. In related to cancer biology, PTHrP is shown to be responsible for hypocalcaemia malignancy [5,6]. Now, Kir et al. put forward the function of PTHrP in cancer biology and demonstrates that tumor derived PTHrP stimulates thermogenic gene expression in adipose tissues and increases resting energy expenditure in mice by browning of white adipose tissues [1]. These data reveal a novel role of PTHrP in hyper metabolism during malignancy. However, injection of PTHrP alone in normal mice is not sufficient to initiate muscle atrophy suggesting that other tumor-secreted factors work in concert with PTHrP to induce muscle wasting. Nonetheless, it appears that white adipose tissue browning is critical in contribution to the adverse effect of cachexia. Similarly, Petruzzelli et al. also shows that browning of adipose tissues is an early event in cancer cachexia [2]. They demonstrate that adipose tissue browning is mainly caused by chronic inflammation and increased cytokine IL-6. IL-6 mediates the adipose tissue browning largely through β-adrenergic activation. Accordingly, β3-adrenergic receptor blockade or nonsteroidal anti-inflammatory drugs efficiently ameliorate the severity of cancer cachexia in their tumor mouse models. Yet, blocking of IL-6 alone in human cancer patients is ineffective in protection against the loss of lean mass [7]. Collectively from both studies, it appears that white adipose tissue browning is only one of the mechanisms contributing to cachexia and it is not a compensatory mechanism in response to loss of insulating capacity. Other tumor-derived factors, particularly for those responsible for skeletal muscle atrophy, remain to be determined.

These recent discoveries open up a new paradigm for the development of therapeutic regimen for cancer patients with cachexia. Targeting these new factors for inhibiting white adipose tissue browning might help to ameliorate the adverse effect from cancer cachexia and improve patient survival. In addition, the understanding of the underlying mechanism of this process also beneficial for application in other diseases such as obesity and diabetes mellitus in promoting weight loss and improving insulin sensitivity. However, extreme cautions have to be taken into consideration while using these potential candidates for drug development. First, it is unclear whether the browning effects of PTHrP or IL-6 are effective only in the settings of malignancy where other unidentified tumor-derived factors are essential to exert synergistic effects for cachexia. For instance, there is no strong correlation for patients with primary hyperparathyroidism that show metabolic abnormalities [8]. Secondly, off target effect may be an issue that affects whole body tissue homeostasis. Both PTHrP and IL-6 have multiple biological functions for our body. In the case of PTHrP, an analog is currently under late stage of clinical trial as an anabolic agent for treatment of osteoporosis by intermittent administration. Yet, a long-standing paradox of PTH/PTHrP regarding their contradictory effects (sustain vs. intermittent) to bone turnover is still not fully understood. It is therefore conceivably to speculate that using neutralizing tumor-derived PTHrP antibodies as a treatment for cancer cachexia may affect total bone mass accrual.

To conclude, hyper metabolism induced by cancer cachexia is deleterious and identifying tumor-secreted factors responsible for adipose tissue browning is only one of the aspects. Many more factors also contribute to this condition in causing metabolic abnormalities. Until we identify a full profile of factors that causes this complication by tumors, a lot more work should be continue in this area in order to develop an effective therapeutic treatment. The next focus should be searching for factors that cause muscle atrophy, which is another hallmark of cachexia.

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