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CACHEXIA & BROWN FAT: A BURNING ISSUE IN CANCER

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Abstract

Cachexia, a progressive weight loss in cancer patients that results from tumor-induced energy wasting, is a serious problem that interferes with response to treatment and affects quality of life. Recent studies suggest that thermogenesis of adipose tissues is involved in energy wasting and also point to a link between the atrophy of fat and muscle. Tumor-derived PTHrP has emerged as a key molecule playing multiple roles in cachexia, from fat “browning” factor to potential therapeutic target.

Keywords

Cancer cachexia; adipose tissue; browning; thermogenesis; skeletal muscle atrophy

Cachexia is a wasting syndrome characterized by the loss of adipose and skeletal muscle tissues that leads to profound weight loss. Nearly half of all cancer patients suffer from cachexia [1]. The development of cancer-related cachexia is a negative prognostic factor for overall survival and is the direct cause of at least 20% of all cancer deaths [1]. The uncontrolled weight loss causes frailty in patients, limits their physical activity and thereby decreases their quality of life. Cachexia also limits cancer therapy. Not only it often delays the initiation and completion of aggressive therapies, but also interferes with responses to treatment. It is likely that effective anti-cachexia therapies may substantially benefit a vast group of cancer patients.

The cachexia problem is often considered as an unfortunate consequence of cancer and frequently overlooked. However, it is now becoming increasingly appreciated that cancer management should involve combined anti-tumor and anti-cachexia therapies, which could have synergistic effects on enhancing response rates and improving quality of life [2]. Unfortunately, there is currently no effective therapy against cancer cachexia and the underlying molecular mechanisms are still poorly understood.

An imbalance in energy metabolism is considered as the critical trigger for cachexia [1]. Tumors stimulate hypermetabolism in host tissues and lead to inappropriate energy

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expenditure [1]. Although in cancer patients this is usually accompanied by reduced food intake, cachexia is fundamentally different from malnutrition. Cachectic patients may eat less, but they are also in a permanent state of negative energy balance that cannot be reversed by nutritional supplementation. The increase in basal metabolic rate is the key culprit in the wasting problem.

Browning of Adipose Tissue and Adaptive Thermogenesis in Cancer Cachexia

Increased thermogenic activity of adipose tissue was shown to contribute to the accelerated energy expenditure and resultant weight loss in mouse models of cancer cachexia [3–6]. There are two types of known thermogenic adipocytes: brown and beige cells. Both of these cells burn sugars and lipids to generate heat and to help maintain body temperature through adaptive thermogenesis. This process involves the uncoupling of mitochondrial respiration, mediated by the uncoupling protein 1 (UCP1), a protein expressed only in thermogenic fat (Box 1). Other futile metabolic cycles including a creatine-driven substrate cycle may also contribute to thermogenesis [7].

Box 1

Uncoupling of mitochondrial respiration

The electron transport chain uses the flow of electrons to transport protons across the mitochondrial inner membrane generating a proton gradient. ATP synthase allows the return of protons to the matrix and uses the energy released by the proton flow to generate ATP through a phosphorylation reaction. Alternatively, uncoupling proteins can channel protons back to the matrix without harvesting their energy. The uncoupling of proton gradient from ATP generation can relieve oxidative stress in the mitochondria and prevent generation of reactive oxygen species. Uncoupling Protein 1 (UCP1) is only expressed in brown and beige fat and specializes in thermoregulation. In activated brown fat, uncoupling by UCP1 dramatically speeds up cellular respiration and the release of chemical energy in the form of heat (Figure I).

Figure I (Text Box).

Uncoupled respiration in fat tissue leads to hypermetabolism.

Unlike white fat cells, which specialize in storing lipids, brown and beige cells express high levels of UCP1 and contain large quantities of mitochondria. While brown adipose cells are the major constituent of brown fat tissue, mainly located in the interscapular and perirenal regions in rodents, pockets of beige cells reside within many white fat depots. Exposure to cold or sympathetic stimulation can increase the number of beige cells and the expression of thermogenic genes in white fat tissue through a process termed “*browning*”. It was recently shown that browning of white fat depots contributes to energy wasting in cachexia. Loss of PRDM16, a transcriptional coregulator essential for the browning process [8], ameliorates adipose wasting in tumor-bearing mice [3]. Blockade of β -adrenergic receptors, which set the sympathetic tone and thermogenic capacity in fat tissue, also shows similar effects [4]. Importantly, the browning response is not due to a cold challenge that tumor-bearing mice may experience. Tumors still activate a thermogenic program under thermoneutrality, when there is no need for thermoregulation to maintain body heat [4]. Both brown and beige fat cells are also found in humans and likely play an integral role in energy homeostasis [9, 10]. Evidence exists for activated brown fat in at least some cachectic patients, including reports of larger peri-adrenal brown fat depots and increased UCP1 expression in white fat tissue [4, 11]. Future prospective studies must test the prevalence and degree of adipose tissue browning using serial tissue biopsies from cancer patients.

How tumors trigger the browning of fat tissue is being unraveled. Parathyroid hormone-related protein (PTHrP), a tumor-derived small polypeptide that modulates calcium homeostasis, promotes fat browning in mice bearing tumors. Neutralization of PTHrP or loss of its receptor in fat cells blocks the browning and wasting of fat tissue and suppresses tumor-induced hypermetabolism, without changing circulating calcium [3, 12]. Elevated levels of circulating PTHrP were detected in a subset of patients with metastatic colorectal and lung cancers exhibiting signs of cachexia. Patients positive for PTHrP showed reduced lean body mass and an increased metabolic rate. This argues that PTHrP may mediate energy wasting and also contribute to the loss of lean mass in cachexia [3]. Although possessing a much lower browning activity than PTHrP, IL6, a cytokine long implicated in wasting, was also described to play a role in browning [4]. Knockdown of IL6 expression in tumors and neutralization of IL6 with specific antibodies prevents browning of white fat and rescued the loss of fat mass. IL6 receptor knockout mice are also resistant to the browning and atrophy of fat tissue [4].

The Interplay of Adipose Wasting and Skeletal Muscle Atrophy

Tumor-driven depletion of fat tissues is not due to a drop in the number of fat cells but to a decrease in lipid stores. While typical white fat cells harbor a single large lipid droplet, tumors promote the emergence of multilocular cells with several smaller droplets. These thermogenic cells (e.g. beige cells) are also enriched for mitochondria and UCP1 (Figure 1). At the same time, tumors also cause atrophy of skeletal muscle fibers. Muscle wasting is caused by unbalanced protein synthesis and degradation in favor of the latter. Pathways of protein degradation are induced by inflammatory cytokines that are secreted by tumors and immune cells, such as TNF α and IL1 (Figure 1) [1].

The breakdown of lipids into fatty acids is a crucial step in adipose wasting, and loss of lipases ATGL and HSL and subsequent deficiency in lipid breakdown improves fat mass. Quite interestingly, it also preserves muscle tissue in tumor-bearing mice, suggesting a link between the atrophy of fat and muscle tissues [13]. In fact, a decrease in muscle mass is often seen at later stages of cachexia, after the loss of fat in mouse models and also in certain cancer patients [14]. Similarly, neutralization of tumor-derived PTHrP preserves both fat and muscle mass and improves muscle strength [3]. The PTH/PTHrP receptor is not expressed in muscle fibers. However, the loss of PTH/PTHrP receptor in fat cells preserves skeletal muscle mass and function in tumor-bearing mice [3, 12]. Likely, PTHrP-induced fat tissue-derived molecules including adipokines, free fatty acids and other metabolites indirectly mediate this crosstalk (Figure 1) [13]. Recent studies on wasting associated with infection provided further evidence for this indirect regulation. In the context of infection, the microbiome *E. coli* can translocate to adipose tissue and promote production of IGF1, a hormone that induces muscle growth and antagonizes wasting [15]. Brown fat transplantation in rodents also elevates circulating IGF1 [16]. A tumor-driven decrease in IGF1 output of fat tissues may partly explain the link between the atrophy of fat and muscle (Figure 1).

Concluding Remarks

Cachexia in cancer and other chronic diseases remains a major unmet medical need. There is a need for new therapies against the wasting syndrome. Elevated systemic inflammation has been implicated in cancer cachexia, but anti-cytokine therapies are generally ineffective. Recent studies described an important role for adipose tissue thermogenesis in energy wasting. The hormone PTHrP emerged as an inducer of adipose browning and as a potential mediator of cachexia, at least in certain cancer patients. Other tumor-derived cachectic molecules with similar effects are likely to exist. New therapies that target these secreted factors and block fat thermogenesis can potentially be used to fight cachexia and hence improve patient survival.

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Figure 1. Tumors drive the wasting of adipose and muscle tissues

Tumor-derived parathyroid hormone-related protein (PTHrP) and interleukin 6 (IL6) promote the browning and depletion of white fat tissue. Typical white fat cells with a single large lipid droplet are replaced by multilocular beige cells containing several smaller droplets and a higher number of mitochondria. Inflammatory cytokines such as tumor necrosis factor α (TNF α) and interleukin 1 (IL1) activate protein degradation in muscle tissue, which shrinks the cross-sectional area of muscle fibers. Muscle atrophy is linked to the wasting of fat tissue through crosstalk mechanisms, likely involving fat-derived adipokines, free fatty acids (FFA) and other metabolites. Reduced insulin growth factor 1 (IGF1) production by fat tissue may also contribute to muscle wasting.