ON CANCER-ASSOCIATED CACHEXIA

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Malignant tumors have the ability to induce a chronic and systemic inflammatory environment that gives rise to cachexia. Metastatic disease can in fact be potently active at inducing cachexia, with onset occurring in the presence of remarkably little overall tumor burden. The efficient induction of cachexia can be explained by the fact that during metastasis, hematogenous tumor cells have the opportunity to closely interact with—and activate—leukocytes. Systemic distribution of these activated inflammatory leukocytes are a source of chronic inflammation. Specifically, these inflammatory nuclei relay “danger” signals to the central nervous system (CNS) by way of the hypothalamus. Signals sent from the hypothalamus mobilize a “fight-or-flight” response, which includes induction of a hypermetabolic state, de novo synthesis of glucose (gluconeogenesis) and muscle breakdown (as a source of precursors for gluconeogenesis).

An acute “fight-or-flight” response may be crucial to providing enhanced access to energy reserves during an emergency. Chronic activation of this response, however, would be expected to have serious and negative consequences over an extended period of time, notably the excessive loss of muscle tissue associated with ongoing gluconeogenesis. This is indeed the situation with cachexia. The unresolvable presence of metastatic tumor results in a continual activation of inflammatory danger signals. The CNS response to the chronic inflammation resulting from metastatic tumor becomes life-threatening as progressive muscle atrophy begins to weaken cardiopulmonary function. The wasting of muscles involved in cardiopulmonary func-

Figure 1. An artist impression (circ. 1840) of a man with a massive tumor. The image illustrates the fact that substantial tumor burden can be accommodated without lethal consequences. Where tumors do not cause obstruction or disruption to vital organ function, the disease may not be life threatening. Conversely, a relatively small tumor burden can cause the insidious and deadly complication of cachexia. In the recent study where patients were treated with an anti-IL-1α antibody, in patients showing the most severe symptoms of cachexia (i.e. greater than 8% weight loss in six months prior to study), none had a total tumor burden greater than 5 cm.
The muscle wasting from cachexia causes death by compromising vital cardiopulmonary function. Degenerative loss of musculoskeletal tissue and decreased cardiopulmonary performance is naturally associated with weakness, fatigue, anxiety and diminishment in life quality—the hallmark symptoms of cachexia (Figure 2). In addition to muscle wasting, anxiety onset is also the direct result of CNS disturbances by inflammatory mediators\(^4\). A causal link between inflammation and anxiety has come from studies in which patients received cytokines as immunotherapy, including therapy for cancer patients. Use of IL-1, interferon or IL-2 therapeutically has been shown to induce a variety of neuropsychiatric symptoms, such as anxiety, depression and irritability. These symptoms can be so severe that they are justification for discontinuation of therapy\(^5\). These responses to cytokine therapy have in fact been linked to induction of ACTH and cortisol, directly implicating the hypothalamus\(^6\).

The insidious, irreversible onset of cachexia is thus a dreaded and perhaps singularly most important disease complication across all forms of cancer.

Compromised cardiopulmonary performance (i.e. decreased ventilation) in cachexia results from the loss of chest, diaphragmatic and even abdominal musculature (Figure 3). Together, these muscles coordinate to develop the negative and positive pressure changes in the thoracic cavity necessary for the acts of inspiration and expiration, respectively.

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**Figure 2.** Unrelenting, chronic inflammation results in loss of crucial skeletal muscle. Arrows suggest causal relationships. Muscle loss, compromised cardiopulmonary function and anxiety result in a diminished quality of life and can eventually lead to death.
Figure 3A. (Above) Integrity of external and internal intercostals and their extensions are critical for inspiration and expiration, respectively. Arrows overlaying the muscles show the direction of muscle contraction that results in expansion or contraction of the thoracic cavity. Muscles used for inspiration include external intercostal and diaphragmatic muscles. The external intercostal muscles contract to pull the ribs outward, increasing the width/volume of the thoracic cavity; this is done in coordination with diaphragm muscles, which contract to expand the vertical dimensions of the thoracic cavity and elevate the lower ribs. The result of overall enlargement of the thoracic cavity is a reduced intra-thoracic pressure, which draws air into the lungs. Relaxation of the external intercostal and diaphragm muscles permits so called “elastic recoil” of the lungs, which constricts the thoracic cavity. The internal intercostal muscles can facilitate active expiration by pulling down on the ribcage, compressing the thoracic cavity and creating the pressure to expire air.

Figure 3B. (Left) The dramatic absence of significant pectoral muscle permits visualization of the underlying loss of intercostal muscles and other muscles crucial for pulmonary function. The loss of muscle in this patient can be expected to translate into considerable cardiopulmonary dysfunction (patient in image suffers from Graves’ disease).
Wasting of chest, diaphragm and abdominal muscle has significant consequence not only for breathing but also for other important functions that affect quality of life. These non-respiratory functions are several fold, including compressing the esophagus at the esophageal hiatus to prevent acid reflux and increasing intra-abdominal pressure to aid in expelling urine and feces.

Loss of respiratory musculature results in decreased ventilation in the lungs, which is further exacerbated by other comorbidities. Fluid accumulation in lung parenchyma and alveolar tissues may occur for a variety of reasons, such as venous congestion that occurs in dependent portions of the lungs of patients who spend prolonged periods of time in bed (hypostatic pneumonia) or as a result of deteriorating cardiac function. Low levels of serum albumin, resulting from malnutrition, lead to a decrease in oncotic pressure and further worsen the pulmonary edema. This fluid accumulation, on top of already poor cardiopulmonary performance, creates a downward spiral, from which many cachexics ultimately do not recover (Figure 4).

Fluid accumulation, however, also creates an environment ripe for infection. Cancer-cachexia patients often succumb to pneumonia-related complications as a result of wasting of respiratory and cardiac muscle. In one of the few studies evaluating the causes of death in cancer patients, Inagaki et al. reported that 24% of 816 cancer patients analyzed postmortem had died of pneumonia.

The loss of muscle due to cachexia is a common natural history of cancer: it has been reported that as many as 80% of advanced cancer patients suffer from cachexia. CNS control of energy balance and muscle metabolism has emerged as a primary defect in the orchestration of errant and chronic muscle breakdown in cachexia. Considering the normal physiological interdependence between muscle and brain, it is not surprising that a CNS defect is a central feature in muscle wasting in cachexia.

Figure 4. Reduced capacity of respiratory muscles results in compromised pulmonary function. Fluid accumulation in airways and alveoli further reduces the efficiency of gas exchange. As respiratory muscles excessively weaken, loss of cardiopulmonary and physical function can rapidly decline.
The CNS has a unique physiological dependency on muscle—which is the only source of food-stuff for the brain in times of limited food availability. With normal nutrition, glycogen reserves in the liver are built up, and then exploited as needed as a source of metabolic energy supply. Glycogen breakdown into glucose is a primary source of fuel for energy demands for virtually all tissues. Most tissues, however, can do without glucose and can oxidize free fatty acids in circumstances of limited stores of glycogen, and low plasma glucose levels. Neuronal cells of the CNS, however, are critically dependent on glucose as an energy source. The absence of glucose in the plasma results in rapid neurological starvation, coma and death.

Unfortunately, the biochemical pathways necessary to synthesize glucose from fat are absent in humans. So even in humans that have good overall energy reserves in the form of adipose tissue, running short on glycogen represents a crisis for energy supply to the CNS.

In times of low caloric intake or starvation—when glycogen reserves are depleted—there are limited alternatives to provide energy to the brain (Figure 5). The enzyme machinery does, however, exist to degrade muscle proteins into amino acids, and to convert these free amino acids into the precursor materials needed to synthesize glucose (gluconeogenesis). In dire circumstances of limiting nutrition, muscle protein is in fact the only possible source of metabolites from which glucose can be synthesized.

**Figure 5.** The CNS is the crucial recipient of glucose synthesized from the amino acid breakdown products of muscle. It seems appropriate, therefore, that the CNS is responsible for orchestrating the metabolic signals that up- or downregulate the enzymatic pathways that control muscle breakdown and gluconeogenesis. In times of starvation, when the CNS is desperate for glucose, it must sacrifice muscle tissue to maintain integrity of the brain—and survival of the organism\(^1\). (AA = amino acids; • hormones, other mediators that stimulate muscle breakdown.)
Figure 6. (Above) The hypothalamus monitors for crisis or danger signals. This command center of the CNS is able to monitor for low plasma glucose levels, adrenalin and other peptide danger signals, such as interleukin-1. In response to crisis, the hypothalamus mobilizes muscle tissue as a source of precursors in the de novo synthesis of glucose\textsuperscript{12}.

(Below) (a) Vascular endothelial cells in capillaries normally form tight junctions. (b) The fenestrated vasculature in parts of the hypothalamus enable direct monitoring of the blood for danger signals. Gaps or pores in the vascular endothelium of hypothalamic capillaries allows close interaction between hypothalamic neurons and substances, such as IL-1, in the bloodstream\textsuperscript{13}. 

\textbf{Trauma, Crisis, Stress}
The brain has the discretionary power to sacrifice muscle tissue in order to preserve the fate of the CNS. But the brain can mobilize muscle protein as a source of emergency energy supply not only in times of low nutrient availability, but also more generally in times of crisis.

In the event of trauma, for example, rapid unsuppressable gluconeogenesis ensues. Trauma, such as burns, blunt injury, postoperative injury, or even highly stressful situations results in a hypermetabolic state with an extraordinary dependence on glucose as an oxidation (energy) source. The classic “fight-or-flight” response, where a surge in adrenalin helps prepare the body for danger, is also a situation where metabolic energy becomes focused on glucose consumption, including that synthesized from precursors from muscle-derived protein.

Brain and muscle are thus inextricably linked: In times of crisis, the CNS mobilizes muscle protein reserves, while muscle integrity requires that the CNS spares the muscle from catabolism except in only the most necessary circumstances. The brain is thus the gatekeeper of muscle homeostasis.

The role of the hypothalamus in responding to crisis or danger signals is highlighted by the fact that it is not isolated behind the blood-brain barrier. The hypothalamus contains a rich capillary network that enables intimate contact between inflammatory mediators and neuronal cells. The capillaries are characterized by vascular endothelium with gapped junctions. This fenestration of the capillaries enables the hypothalamus to conduct direct surveillance of blood constituents. In this way, the hypothalamus monitors circulating substances, such as peptides and glucose, in order to play its role in homeostasis. Considering its crucial involvement in monitoring blood glucose levels, the hypothalamus is a logical site to regulate energy balance and muscle metabolism (Figure 6).

In the brain, it is the hypothalamus that acts as the central command for regulating energy balance and muscle metabolism. β-adrenergic receptors (BAR) present in the hypothalamus allow the rapid responses to stress and crisis in response to adrenalin. The presence of IL-1 receptors in the hypothalamus allows detection of inflammatory signals (Figure 7). Detection of IL-1 provides a mechanism to detect stress or crisis that is independent of the adrenalin system.

**Figure 7.** Immunohistochemical staining of hypothalamus reveals intense expression of interleukin-1 receptor in the arcuate nucleus. Arrows below indicate areas of intense IL-1 receptor staining. V3 designates the third ventricle, which occupies space adjacent to the arcuate nucleus. Neurons of the arcuate nucleus play a central role in the regulation of appetite and energy homeostasis14.
In cachexia, signals delivered to CNS via IL-1 receptor signaling direct the brain to inappropriately tap muscle as an energy resource. Even in the presence of adequate nutrition, and in the absence of obvious stress or trauma, the brain is continuously mobilizing muscle breakdown. In cachexia, this is because the brain is constantly triggered into crisis mode by circulating inflammatory cells that have become activated by the presence of metastatic tumor.

Mechanisms by which chronic inflammation can undermine CNS control of muscle metabolism have been elucidated. Signals originating from the arcuate nucleus of the hypothalamus orchestrate the CNS role in regulating muscle metabolism. In the presence of systemic, chronic inflammation, the arcuate nucleus picks up unrelenting inflammatory signals that notify of crisis.

While chronic inflammation has for some time been considered to mediate cachexia, only recently has a clear mechanism been described that involves IL-1 signaling at the level of the hypothalamus. Neuronal pathways triggered by IL-1 signals at the hypothalamus, have been shown to be able to account for the CNS-derived signals that stimulate muscle breakdown (Figure 8)\textsuperscript{15}.

The cause of death in advanced cancer is multifactorial. Infiltration of tumor into organs and disruption of vital organ function—carcinomatosis—can and does occur. But as seen in the recent study using the anti-IL-1\(\alpha\) antibody in advanced cancer patients, patients commonly have little evidence of sufficient tumor burden to cause life-threatening disruption of organ function.
A relatively small amount of tumor burden, in the form of metastatic tumor cells circulating in the vasculature, can be highly efficient in providing the danger signals that dysregulate hypothalamus function. A small amount of tumor burden driving a lethal cachexia seems counterintuitive. Yet new methods for detecting and even enumerating tumor cells present in the blood of cancer patients reveals that even with no visible presence of solid tumor burden, significant numbers of circulating tumor cells may be present in the blood\(^\text{16}\). Anywhere from several to several thousand tumor cells may be present in each milliliter of blood in a cancer patient that otherwise has little radiological evidence of disease.

Circulating tumor cells are known to bind leukocytes in the blood. The mechanism by which this occurs likely involves lectin interactions between the heavily glycosylated proteins on the surface of tumor cells and corresponding glycoprotein moieties on leukocytes, particularly platelets.

In cachexia, the presence of tumor-platelet aggregates in the blood can deliver the chronic danger signals that mediate the disease. The adherence of blood-borne tumor cells to platelets results in activation of platelets, similar to what might occur during trauma or injury. Activation of platelets makes them “sticky” and interactive with the vascular endothelium. Increased interaction of platelets enables their surface expressed IL-1\(\alpha\) to bind interleukin-1 receptor (IL-1R) on vascular endothelial cells, including those of the fenestrated microvasculature of the hypothalamus. IL-1R is also present on the neuronal cells of the hypothalamus, and signaling through these receptors can trigger the cascade of danger signals that ultimately leads to muscle breakdown.

The results of the recent trial using an anti-IL-1\(\alpha\) antibody to block cachexia indeed provided further insight into the role of IL-1\(\alpha\) in clinical progression of cachexia. These findings also highlighted the relative importance of cachexia as compared to overall tumor burden in advanced cancer patients—where imminent concerns for health and well being may be more related to the process of cachexia rather than tumor burden per se.

One patient, for example, had only 4.7 cm total tumor burden, yet had lost 20\% of body weight prior to entering study (total tumor burden is calculated by adding together the major axis of each target lesion in the patient). Unintentional rapid loss of 20\% of body weight in an advanced cancer patient likely indicates that the patient is rapidly declining clinically. In response to treatment with anti-IL-1\(\alpha\) antibody, the patient’s muscle mass appeared to normalize, as evidenced by an 11\% gain (2.73 kg) of muscle within 8 weeks. Nearly two-thirds (12/18) of patients analyzed responded to three infusions of anti-IL-1\(\alpha\) antibody therapy, averaging a 1.57 kg increase in muscle tissue. In patients showing the most severe symptoms of cachexia (i.e. greater than 8\% weight loss in six months prior to study), no patient had a total tumor burden greater than 5 cm.

Chronic danger signals resulting from circulating inflammatory tumor-platelet microemboli result in ongoing disruption to normal hypothalamic control of metabolism. The incessant mobilization of energy stores in response to the chronic crisis leads to progressive muscle wasting. The ongoing wasting of muscles can not be tolerated indefinitely, and leads to severe clinical complications and death in advanced cancer patients. Remarkably, in the presence of little solid tumor burden, adequate numbers of circulating tumor cells may be present to trigger the disease.

Targeting IL-1\(\alpha\) with a therapeutic antibody appears to disrupt the systemic inflammation associated with dysregulated CNS control of muscle metabolism. Blocking IL-1\(\alpha\) on platelets and other inflammatory cells may provide a means for directly interrupting the danger signals emanating from circulating tumor cells. Recent clinical observations using an IL-1\(\alpha\) antagonist suggest that this might represent a means of normalizing muscle mass, and offer the possibility of a novel approach to manage chronic inflammation in advanced cancer patients.
REFERENCES


