

PBL SEMINAR (Biochemistry & Molecular Biology Discipline)

MALIGNANT CACHEXIA – An Overview

What is Cachexia?

Cachexia describes the characteristic wasting/ weight loss often seen in cancer patients. Indeed weight loss is a common feature in advanced cancer. Thus, unexplained weight loss in many sick patients may be a sign of malignancy.

The weight loss is largely from skeletal muscle and adipose tissue, with relative sparing of visceral protein (i.e., liver, kidney, and heart.)

In general, cachexia is a clinical feature of many malignant diseases presenting at an advanced stage. Some of the clinical features of cachexia include: **Anorexia, Lethargy, Weight loss, Muscle weakness, Anemia and Pyrexia.**

What are the possible causes of Cachexia?

Decreased appetite and food intake, production of catabolic factors secreted by certain tumors and other autoimmune cytokines, contribute to but do not entirely account for the cachexia in affected patients.

Indeed, the loss of taste and the malaise that accompanies many malignant diseases may contribute to poor food intake leading to malnutrition, but these factors do not fully explain the cachexia of malignancy.

Although many cancer patients may have a negative nitrogen balance, others who are in positive nitrogen balance may show caloric deficit.

Most tumors commonly exhibit high rates of glycolysis and release lactate in the presence of oxygen, however the energy requirement of the tumor does not explain weight loss because weight loss can occur with even small tumors.

In the cachexia accompanying malignant diseases, caloric expenditure remains high, with an elevated basal metabolic rate despite reduced dietary intake; this indicates that the weight loss results from a profound systemic derangement of host metabolism.

It is important to note also that HIV infection, congestive heart failure, and a host of other degenerative diseases as well as aging and surgery can result in the body shifting from a healthy anabolic cell-replacement metabolism into a catabolic wasting state.

Catabolic wasting state is characterized by severe weight loss (due to depletion of adipose tissue and muscle breakdown), anorexia, weakness and lethargy.

Cachexia-Anorexia Syndrome (CAS):

In advanced cancer the catabolic state, which ultimately results in weight loss is referred to as Cachexia-Anorexia Syndrome (CAS).

This is a catabolic state in which abnormal metabolism causes a degree of weight loss that cannot be attributed to decreased caloric intake alone.

Indeed, even with adequate nutrition, weight loss may occur because the body cannot utilize the nutrients from food properly.

CAS is caused by chemical messengers, also called immune cytokines, which are produced by the tumor itself, and by the body's immune system in response to the tumor.

These chemical messengers include (but not limited to): **Tumor necrosis factor, interleukin-1, interleukin-6, interferon gamma, and proteolysis inducing factor.**

It is the effect of these chemicals on the brain, general body metabolism and skeletal muscle that results in CAS.

Some of these chemical messengers act on the hunger centres in the hypothalamus and the frontal cortex to dull the brain's sensitivity to hunger signals from the body, and to inhibit its ability to generate an appetite.

These chemical messengers also act on the liver, pancreas and peripheral tissues, causing abnormalities in the metabolism of carbohydrates, lipid and protein.

The most significant of these is an increase in skeletal muscle breakdown. Instead of using fat for energy production, the body of a patient with CAS preferentially uses skeletal muscle protein as an energy source.

Although the liver continues to produce an abnormally large number of "reactive proteins", these are not the type required to rebuild skeletal muscle, and so muscle is not replaced.

Furthermore, the normal body adaptation to starvation (decreased basal metabolic rate and preferential use of fat as an energy source) does not occur in a patient with CAS. Instead, there is usually increased resting energy expenditure (i.e., increased BMR).

In other words, when at rest, a cancer patient with CAS will burn more calories than a person without cancer, using body protein as the energy source.

Some of the cytokines include the following (**SEE Figure 1**) and note the following:

1. **Interleukin-1** activates proteolysis (breakdown of proteins) in skeletal muscle.
2. **Interleukin-6** stimulates synthesis in the liver of a number of hepatic proteins called **acute phase reactants**. Acute phase reactants include fibrinogen, complement proteins, some clotting factors, and α_2 -macroglobulin, which are presumed to play a role in defense against injury and infection.
3. **TNF- α** suppresses synthesis of fat in adipose tissue, prevents uptake of circulating fat by inhibiting lipoprotein lipase, stimulates lipolysis, inhibits release of insulin, and promotes insulin resistance.

These cytokines appear responsible for much of the wasting seen in chronic infections and malignancy.

Malignancy and Metabolic changes:

In general cancer can be considered as a physiological stress on the organism. Other types of physiological stress include injury, surgery, renal failure, burns, and infections.

These stresses cause increase in the **levels of blood Cortisol, Glucagon, Catecholamines, and Growth hormones.**

In addition the patient is usually resistant to insulin. Basal metabolic rate, blood glucose, and free fatty acid levels are elevated.

For reasons not completely understood, the intracellular muscle Glutamine pool is reduced, resulting in reduced protein synthesis and increased protein breakdown.

(The reversal of protein breakdown in such patients is quite difficult, although it is common to replace amino acids, glucose, and fat by infusing solutions of these nutrients intravenously. However, these solutions lack glutamine, tyrosine, and cysteine because of stability and solubility constraints. It has been suggested that supplementation of these amino acids, perhaps by the use of more stable dipeptides, may help to reverse the catabolic state resulting in cachexia.)

Some other phenomena may contribute to the metabolic disturbances in CAS. Some tumors synthesize and secrete biologically active peptides such as Adrenocorticotrophic hormone (ACTH), nerve growth factor, and insulin-like growth factor, which could modify the endocrine regulation of energy metabolism.

Metabolism in Cancer cells:

Cancer cells have a distinctive type of metabolism. Although they possess all the enzymes required for most of the central pathways of metabolism, cancer cells of nearly all types show an anomaly in the integration of the Glycolytic pathway and the TCA cycle.

Furthermore two important points must be noted.

During metabolism: -

1. **The rate at which cancer cells consume O₂ is lower than the values for normal cells.**
2. **Cancer cells tend to utilize about 5 to 10 times as much glucose as normal tissues, and the cancer cells convert most of the glucose into lactate, even in the presence of O₂.**

The normal allosteric factors regulating the rate of glycolysis to match the rate of utilization of pyruvate by the TCA cycle, i.e., through the Pasteur effect, are defective or altered in cancer cells.

(Pasteur effect states that the rate of glycolysis is indirectly suppressed in the presence of O₂).

The most important systemic effect of this metabolic imbalance in cancer cells is the utilization of a large amount of blood glucose and the release of correspondingly large amounts of lactate into the blood.

The lactate so formed is then recycled in the liver to produce blood glucose again by the process of **Gluconeogenesis**, exactly as occurs during heavy muscular work – the **Cori cycle** and the **Alanine cycle** (See **Figure 2**).

Since the **formation of a molecule of glucose from lactate requires input of six molecules of ATP in the liver**, whereas the cancer cell produces only **two molecules of ATP per**

molecule of glucose converted into lactate, the cancer cell may be looked upon as a **metabolic parasite, that depends on the liver for a substantial part of its energy**. Large masses of cancer cells thus can be a considerable metabolic drain on the host organism, in addition to causing other local and systemic effects.