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A Molecular Approach to Cancer Cachexia

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Hippocrates described a syndrome of wasting and progressive inanition among patients who were ill and dying. The Greek words kakos, meaning "bad things" and hexus, meaning "state of being", have led to the term cachexia to describe this syndrome. Cachexia, defined as accelerated loss of skeletal muscle in the context of a chronic inflammatory response, can occur in the setting of cancer as well as in chronic infection, AIDS, heart failure, rheumatoid arthritis and chronic obstructive pulmonary disease [1].

The term cachexia refers to the dramatic weight loss that is characteristic of several systemic diseases including cancer. Cancer cachexia is unresponsive to current medical interventions. Cachexia may arouse as a first symptom of cancer and nearly all cancer patients have lost significant weight loss by the time of death [2]. The weight loss that occurs in cancer cachexia is the result of a net energy deficit which is partly the result of poor oral intake but is also the result of metabolic aberrations that lead to increased basal energy expenditure. The resulting weight loss cannot be adequately treated with aggressive feeding [3, 4]. Cancer cachexia is not a passive event; it is an active response of the host to cancer. It is a symptom of this inflammatory process.

Weight loss is the most obvious manifestation of cancer cachexia and is a marker for both progression of the syndrome and prognosis. In addition to poor prognosis and impaired response to therapy, cachexia may be a direct cause of death [5].

Cancer cachexia is characterized by diminished nutrient intake and progressive tissue depletion, both of which lead to weight loss. Changes in body composition, increasing debility, fluctuations in resting energy expenditure, loss of appetite and at times, an inability to eat for mechanical reasons further characterize this syndrome.

The pathological consequences of cachexia result from muscle wasting. The protein malnutrition leads to a disordered immune system and increased susceptibility to infections [6]. The accompanying malaise and weakness result in decreased quality of life [7].

Understanding of molecular basis of cachexia may help to develop new therapeutic strategies to overcome it. TNF-α and IL-6 are major cytokines implicated in the pathogenesis of cachexia [8]. TNF-α may stimulate catabolism via direct and indirect mechanisms. It alters circulating levels of hormones that regulate muscle growth and affects tissue sensitivity to such factors. It also stimulates production of catabolic cytokines and induces anorexia. Mechanisms by which TNF-α might directly stimulate catabolism is less clear. TNF-α can limit the regenerative response of satellite cells to muscle injury [9] and it may have a direct catabolic effect on differentiated muscle [10] or inhibit myoblast differentiation [11]. The muscle wasting results from increased protein degradation. There are several proteolytic pathways in the skeletal muscle. The most important of them is the ATP-dependent ubiquitin-proteosome pathway. The proteosome degrades a substantial fraction of the newly synthesized proteins in cells. As many as one-third of the newly made polypeptide chains are selected for rapid degradation. The final disposal apparatus in eukaryotes is the proteosome and abundant ATP-dependent protease that constitutes nearly 1% of cellular protein. The proteasomes act on proteins that have been specially marked for destruction by the covalent attachment of multiple copies of a small protein called ubiquitin.

Failure of this protein degradation leads to destructive diseases such as Huntington's disease and Alzheimer's disease. Its overactivity is a special feature of cancer cachexia. The present study showed increased mRNA levels of ubiquitin and proteasome subunits in cancer cachexia. The proinflammatory cytokines are known to upregulate the ubiquitin-proteasome pathway. TNF-α can act directly on muscle cells to stimulate protein loss, an action mediated by nuclear factor-κB (NF-κB) which is a transcription factor. The stimulation of the type 1 TNF-α receptor leads to an increase in reactive oxygen species (ROS) production via mitochondrial electron transport. The mitochondrion is known to be exquisitely sensitive against ROS. In response to ROS mitochondria were found to produce NO, which is also damaging for mitochondria [12]. Buck and Chojkier [13] have shown that antioxidants and nitric oxide synthase blockade inhibits muscle wasting in a mouse model of TNF-α -induced cachexia. NF-κB appears to increase activity of the ubiquitin/proteasome pathway.

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In cachexia, resting energy expenditure is increased, which is largely due to increased heat production. Metabolic cycles that consume ATP and release heat are called futile cycles. Uncoupling proteins (UCP 1-4) are mitochondrial carrier proteins that stimulate heat production by dissipating the proton gradient during respiration across the inner mitochondrial membrane and therefore uncoupling respiration from ATP synthesis. In experimental cancer cachexia, expression of both the UCP2 and UCP3 genes is significantly increased in skeletal muscle of tumor-bearing animals [14]. Interestingly, cancer cachexia also results in upregulation of UCP2 gene in brain, suggesting a potential role of brain as a thermogenic organ [15]. In the cachectic conditions, cytokines seem to be responsible for the increased UCP2 and UCP3 gene expression.

These findings suggest that ubiquitin-proteasome system would be an excellent target for therapeutic intervention.

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