Mechanism of cancer-induced fatigue

Jing-Yu Xu, Yi-Hua Fan, Jun-Ze Geng, Hui-Xin Chen, Zi-Jun Qi, and Xin-Ju Li

***Abstract*—Cancer related fatigue (CRF) is one of the most common and painful reactions in cancer patients. Due to the negative effects of cancer itself and long-term treatment, patients often feel continuous burnout, fatigue and powerlessness in both mental and physical aspects. Fatigue related to cancer and cancer treatment will affect the physical and mental health of cancer patients for a long time and continuously, and it is hard to be relieved through rest. Nowadays, most of the researches focus on the clinical manifestations of patients with cancer, such as pain, nausea and vomiting, weight loss and so on. The fatigue feeling of cancer patients is often one of the most easily overlooked pain symptoms in the treatment process. The influence of CRF on cancer patients may be one of the reasons for reducing the survival time of cancer patients. This paper aims to summarize and explore the pathogenesis of cancer-related fatigue, in order to analyze the related factors of cancer-related fatigue from multi-dimensional and multi-angle, and provide reference for its comprehensive treatment in clinic.**

***Key words*—Cancer related fatigue, Cancer, Mechanism, Energy imbalance**

INTRODUCTION

Cancer related fatigue (CRF) is one of the most common and painful reactions in cancer patients. Due to the negative effects of cancer itself and long-term treatment, patients often feel continuous burnout, fatigue and powerlessness in both mental and physical aspects [1]. Symptoms, such as dizziness and weakness, limb pain, will seriously affect the quality of life of patients [2]. Healthy people can also feel fatigue, which is one of the perceptual senses of the brain [3]. The feeling of fatigue will make people eager to rest and relax, so as to regulate the normal physiological and psychological activities of the human body [4], and keep healthy. However, CRF is quite different. Fatigue related to cancer and cancer treatment is not directly proportional to the degree of fatigue of patients [5]. It will affect the physical and mental health of cancer patients for a long time and continuously, and it is hard to be relieved through rest [6]. Therefore, patients often bear huge pressure and pain, and their daily life is also seriously affected.

Nowadays, researches emerge endlessly on the occurrence and development of cancer, and people's understanding of cancer is also from macro to micro. Most of the researches focus on the clinical manifestations of patients with cancer, such as pain, nausea and vomiting, weight loss and so on [7]. The fatigue feeling of cancer patients is often one of the most easily overlooked pain symptoms in the treatment process. A large number of studies show that the prevalence of CRF is more than 60%, and even studies show that the prevalence of CRF is as high as 90% [8]. CRF is often reported as the most painful symptom of cancer patients [9]. This shows the influence of CRF on cancer patients, which may also be one of the reasons for reducing the survival time of cancer patients. In recent years, the research on cancer-related fatigue is gradually increasing, so this paper aims to summarize and explore the pathogenesis of cancer-related fatigue, in order to analyze the related factors of cancer-related fatigue from multi-dimensional and multi-angle, and provide reference for its comprehensive treatment in clinic.

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MECHANISM OF CANCER-RELATED FATIGUE

Skeletal muscle atrophy and energy metabolism disorders

The reason why the body has a sense of fatigue is mainly due to the accumulation of lactic acid and other metabolites in the muscle, which leads to the decrease of muscle tension and exercise durability [10]. At the same time, the accumulation of carbon dioxide caused by slow metabolism will stimulate the respiratory center and make people feel sleepy. All diseases develop to a certain stage can appear varying degrees of fatigue, and cancer-related fatigue is one of the most serious. Studies have shown that skeletal muscle atrophy, as a part of cancer cachexia, is one of the main causes of fatigue [11]. The decrease of muscle tension limits the level of physical activity of patients and makes them feel powerless; Although the food intake is normal, the patients often difficult to get enough energy supply due to excessive nutrition consumption of tumor [6], so the fatigue is hard to be alleviated.

As the power source of muscle tissue, protein synthesis and metabolism affect the normal physiological function of muscle tissue. Cancer patients with skeletal muscle protein metabolism disorders (increased protein degradation and decreased synthesis), resulting in muscle atrophy. The proteolytic system of skeletal muscle in cancer patients is highly activated, among which the most far-reaching ones are the calcium (Ca^{2+}) dependent protease system and adenosine triphosphate (ATP)-dependent ubiquitin proteasome system (UPS) [12]. In cancer patients, high serum calpain will act as the promoter of myofibrillar protein degradation, resulting in the final disintegration of myofibrils [13−15]; The high expression of UPS will accelerate the ubiquitination of myofibrillar protein, and then S26 protease will decompose it into small peptides to complete the protein degradation process [16]. At the same time, the protein hydrolysis inducing factor (PIF) released by the tumor itself inhibits the initial translation of protein through the phosphorylation of eukaryotic initiation factor 2A (eIF-2a) [17], thus inhibiting the synthesis of protein in

muscle tissue, making muscle tissue unable to obtain the energy to maintain normal metabolism, thus causing atrophy.

In order to maintain the normal operation of body function, besides sufficient material base -Protein, the normal operation of energy converter is also essential. Mitochondria, as the energy processing plant in cells, are the key to the normal metabolism and function of tissues. During the period of muscle atrophy in cancer patients, some researchers found that mitochondrial dysfunction in muscle cells is an important factor leading to the lack of energy supply in patients, including the decrease in the number of mitochondria, the abnormality caused by the dilution of mitochondrial matrix and the decrease in ATP synthesis [18]. Shum Amy et al. have shown that myocyte enhancer MEF2C, a myogenic transcription factor related to ATP synthesis, which targets myoglobin, has been found to be significantly down regulated in cancer mice [19], which indicates that muscle atrophy is related to imbalance of energy metabolism. Due to the high energy metabolism caused by tumor, the energy in muscle tissue is over consumed, and ultimately in a state of energy deficiency for a long time, that is, the income cannot make ends meet. Therefore, patients will have fatigue such as weakness of limbs.

Neuroendocrine disorder

Stress factors. Stress response mainly shows the high activation of endocrine system [20]. Cancer patients often suffer from damage and mental pressure caused by cancer itself, time, money and energy invested in long-term treatment. Appropriate stress can help the body coordinate the function of the body organs to cope with the changes inside and outside the body; However, intense or sustained stress will deplete the ability of endocrine glands and hormone receptors of target cells, which leads to neuroendocrine imbalance in vivo. Cancer patients with chronic stress can constantly generate oxidative stress reactions in vivo, which produce a burst of active oxygen species in tissue cells [21], and eventually leads to the decrease of mitochondrial respiration and energy supply. This will damage the normal aerobic metabolism and muscle endurance of the human body, and further lead to CRF.

Tumor factors. Tumor growth consumes energy, which is due to the rapid undifferentiated growth of tumor by converting glucose into lactic acid [22]. Excessive lactic acid accumulation is one of the causes of muscle tension decline and fatigue; At the same time, other metabolic "wastes" of tumor cells will activate systemic inflammatory response through neuroendocrine regulatory network [23], such as inflammatory factors interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor α (TNF-α). They can activate the hypothalamus pituitary adrenal axis to make the body in a state of oxidative stress, that is, a process of high energy metabolism. For cancer patients, this process will be long-term, patients have to tolerate such a long time of material consumption, and then the body function will be in a low energy state for a long time, such an extreme energy imbalance is an important reason for CRF.

Chronic inflammation and immune disorder

Tumor tissues often show high activity of pro-inflammatory cytokines, which will lead to chronic inflammation for a long time. Excessive inflammatory reaction is bound to continue to activate the human immune system, thus inducing abnormal energy metabolism in cancer patients. For example, IL-6 has been found to induce myofibrillar protein degradation by activating JAK/STAT3 pathway [24], thus causing muscle atrophy and aggravating the occurrence of CRF. Immune and metabolic disorders caused by systemic inflammatory response are often transmitted to the central nervous system through the neuroendocrine network, and then affect the neurotransmitter metabolism, neuropeptide function, sleep wake cycle and other functions in the brain [25]. These comprehensive effects together lead to abnormal sensation and strong mental and physical fatigue in cancer patients. Kamath J's research has proved that there is a correlation between the level of CRF and immune inflammatory markers in cancer patients. Serum inflammatory markers in patients with advanced cancer are at a high level, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), α1 acidic glycoprotein (α1-AGP) and IL-6 [26].

Conclusion

CRF is common in cancer patients, and it is also a major factor affecting the life quality of patients. Because of its complex mechanism of action, involving a variety of physical and chemical system disorders, it is particularly important to understand its pathogenesis related pathways for clinical treatment. In conclusion, the occurrence of CRF is mainly related to skeletal muscle atrophy and energy imbalance, neuroendocrine disorders caused by pressure and tumor, chronic inflammation and immune disorders in vivo. We can find that the common point is the consumption of a large amount of material base in cancer patients. The rapid growth of tumor cells is due to its incomplete differentiation. In order to grow rapidly, tumor cells will absorb more energy than normal human tissues. So, fatigue of cancer patients will be aggravated, caused to extreme weakness.

CRF is the result of a variety of factors, which basically leads to the low-energy state of cancer patients. The fatigue caused by physical weakness and social psychological pressure will further worsen the physical state of patients and make them in the vortex of pain. At present, the research on CRF continues, and multi-dimensional research on CRF should become a topic for more medical researchers.

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