Life Sciences 170 (2017) 56–63

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

TNF-α and cancer cachexia: Molecular insights and clinical implications

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ARTICLE INFO

Article history:
Received 24 September 2016
Received in revised form 27 November 2016
Accepted 30 November 2016
Available online 3 December 2016

Keywords:
Cancer cachexia
Tumor necrosis factor- alpha (TNF-α)
Skeletal muscle wasting
Acute phase response
Metabolic abnormalities

ABSTRACT

Cancer cachexia characterized by a chronic wasting syndrome, involves skeletal muscle loss and adipose tissue loss and resistance to conventional nutritional support. Cachexia is responsible for the reduction in quality and length of life of cancer patients. It also decreases the muscle strength of the patients. The pro-inflammatory and pro-cachectic factors produced by the tumor cells have important role in genesis of cachexia. A number of pro-inflammatory cytokines, like interleukin-1 (IL-1), IL-6, tumor necrosis factor- alpha (TNF-α) may have important role in the pathological mechanisms of cachexia in cancer. Particularly, TNF-α has a direct catabolic effect on skeletal muscle and causes wasting of muscle by the induction of the ubiquitin-proteasome system (UPS). In cancer cachexia condition, there is alteration in carbohydrate, protein and fat metabolism. TNF-α is responsible for the increase in gluconeogenesis, loss of adipose tissue and proteolysis, while causing decrease in protein, lipid and glycogen synthesis. It has been associated with the formation of IL-1 and increases the uncoupling protein-2 (UCP2) and UCP3 expression in skeletal muscle in cachectic state. The main aim of the present review is to evaluate and discuss the role of TNF-α in different metabolic alterations and muscle wasting in cancer cachexia.

Contents

1. Introduction

Cancer cachexia, a metabolic syndrome is characterized by anorexia, loss of weight and decreased muscle strength [1]. Decreased physical activity, poor quality of life, poor performance status, increased risks of cancer treatment and high mortality rates are mainly present in cancer cachectic patient which affects patient's physiological and biochemical balance [2]. Up to one half of all cancer patients may have cachexia and represents a significant decreased physical activity and psychological burden [3]. Cachexia is associated with skeletal muscle protein loss and reduction of body lipid stores during metabolic process. These metabolic changes in cachexia are to some extent facilitated by changes in concentration of hormone present in the circulation including insulin, glucagon and glucocorticoids [4]. In addition, the tumor and host cells

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http://dx.doi.org/10.1016/j.lfs.2016.11.033
0024-3205/

have competition for nutrients which leads to an enhanced catabolic state. Severe alterations in metabolic process are stimulated in the host, including hyper metabolism leading to a reduced energy productivity [5].

Various pro-inflammatory cytokines such as tumor necrosis factor - α (TNF-α), IL-6, IL-8, interferon (IFN)- γ, parathyroid hormone- related peptides (PTHrP) and macrophage migratory factor (MIF) also have important role in cancer cachexia [6]. TNF-α is a cell signaling protein responsible for several metabolic derangements [7]. TNF-α is released by activated macrophages and by many other types of cell such as CD4 +, neutrophils, mast cells, eosinophils and neurons. TNF-α is able to induce apoptotic cell death, cachectic condition and inflammatory response [8]. TNF-α can promote most of the abnormalities found during cancer cachexia, *i.e.*, loss of weight, loss of appetite, increased thermogenesis, alterations in carbohydrate, protein and lipid metabolism, insulin resistance and wasting of muscle by the activation of breakdown of protein [9]. The present review aims to put forth the role of TNF-α in cancer cachexia.

2. Cancer cachexia

Various pathophysiological changes involved in the progress of cancer cachexia are anorexia, loss of body weight, metabolic alterations *i.e.* glucose, protein and lipid metabolism, systemic inflammation, insulin resistance, oxidative stress and muscle protein degradation [10–12]. Several pro-inflammatory cytokines and pro-cachectic factors are considered as mediators of the cachectic process [13]. Various cytokines responsible for the inflammation increase the host systemic inflammatory response and pro-cachectic factors like proteolysis inducing factor (PIF) and lipid mobilizing factor (LMF) have direct catabolic effect on host tissues during cancer cachexia [14]. Table 1 provides an overview of pathophysiological mechanisms of cancer cachexia.

3. TNF-α in anorexia and body weight loss

Anorexia plays a vital role in accounting for malnourishment; perpetually has association with cachexia during cancer. The cytokine involved for the progression of cancer cachexia is TNF-α. TNF-α increases the corticotrophin-releasing hormone (CRH) level and decreases food intake (Fig. 1). It also increases the firing of neurons, which, are sensitive to glucose and, causes the reduction in food intake [15,16].

Body weight loss is the noticeable clinical feature of cachexia in adults [17]. Body weight loss, which is more than 5–10% of original body weight is considered as a definition point for cachexia [18]. Generally body weight loss is responsible for nearly 30% deaths [19]. Different preclinical studies have reported that cytokines have ability to increase loss of body weight. It has been demonstrated that the nude mice showed anorexia, progressive wasting and death when implanted with Chinese Hamster Ovary cells (CHO) in which human TNF gene was used for the transfection in CHO cells [20]. It specifies that TNF-α has important role in the progression of cachexia. Furthermore, the considerable amounts of TNF-α has been detected in the blood of rats with tumor [21]. In contrast, the experimental evidence by Mulligan *et al.* [19] reported that loss of body weight in animals possessing a murine adenocarcinoma (MAC 16) is not associated with the cytokines TNF-α or IL-6 [19]. A possible explanation for this could be that body weight loss occurs due to two major reasons: a) skeletal muscle wasting and b) adipose tissue loss and TNF-α is reported to play a role in both of these [22] (Fig. 1).

Table 1
Various pathophysiological mechanisms of cancer cachexia.

Sr. no.	Pathophysiological mechanisms of cancer cachexia	
	Key mechanisms	Resultant effects
1	Anorexia	Malnutrition
2	Body weight loss	Skeletal muscle loss Adipose tissue loss
3	Metabolic abnormalities (alteration in carbohydrate, protein and lipid metabolism)	Gluconeogenesis, proteolysis, lipolysis
4	Insulin resistance	Muscle protein degradation and muscle wasting
5	Systemic inflammation	Acute phase protein response

3.1. Skeletal muscle wasting

The decrease in the skeletal muscle mass is associated with the decrease in strength, energy and poor quality of life of patient [23,24]. As muscle loss increases, there is a decreased movement and individuality and also hospitalization rate increases [24]. The decreased protein synthesis rates and increased protein degradation rates (protein turnover) is responsible for the loss of skeletal muscle mass. TNF-α activates this wasteful metabolic process [25].

Several experimental evidences from preclinical studies suggest that TNF-α has important role in wasting of muscle during cancer cachexia [26,27]. One experimental finding by Li *et al.* [26] reported that there was decrease in total content of protein, including adult myosin heavy chain fast-type (MHCf), in muscle by time and concentration depending manner, stimulated by TNF-α. MHCf losses were not associated with change in rate of synthesis. This observation suggests that TNF-α stimulates degradation of myofibrillar proteins. Another study has reported that acute treatment with recombinant TNF-α in rats showed increased degradation of protein and decrease synthesis of protein in soleus muscle (red), but not in extensor digitorum longus (EDL) (white) muscle [28]. It has also been reported that there was a decrease of body protein in diseased rats when they were treated with recombinant TNF-α for long time. Redistribution of protein and a marked depletion in content of muscle protein occurs after long treatment with recombinant TNF-α [29]. These findings suggest that TNF-α decreases myofibrillar proteins mRNA levels and induces muscle wasting in later stage of cancer cachexia. Furthermore, the engineered mice lacking in the TNF-α receptor protein type I (TNFR1), when transplanted with Lewis lung carcinoma showed decreased muscle wasting compared with wild-type mice even with similar TNF-α level in serum in both [30]. It is also suggested that TNFR1 subtype is involved in muscle protein degradation rather than TNFR2 and stimulate muscle wasting. Some experimental studies [31,32] reported that catabolism of muscle is stimulated by TNF-α by activation of the ubiquitin proteasome pathway. After an acute, intravenous injection of TNF-α, both free and conjugated ubiquitin and mRNA levels of ubiquitin were increased in the intact rats' limb muscles [31]. These results are in agreements with the study of Llovera *et al.* [33], in which they have reported that TNF-α showed increased in levels of ubiquitin mRNA in excised muscle *in vitro* [33].

TNF-α promotes a complex array of post receptor signaling events which cause pleiotropic, cell-type-specific responses. The response of TNF-α at cellular level is mediated by three major pathways. Out of three pathways, NF-kB induced catabolic signaling plays a key role in protein degradation associated with cachexia. In this pathway, TNF-α activates nuclear factor kappa B (NF-κB) which is a primary mediator for the control of transcription and a major applicant for signaling during catabolism [34]. TNF-α rapidly promotes activation of NF-kB in cells of skeletal muscle, including differentiable myotubes [35,36] and undifferentiable myoblasts [37,38]. TNF-α binds to the type 1 TNF-α sarcolemmal receptor and triggers the events. This receptor is involved in the regulation of protein loss [39].

The activity of protein kinase C (redox-sensitive kinase) is stimulated by TNF-α [35]. Rapid conjugation of ubiquitin to muscle proteins is also caused by TNF-α [36]. These events cause the proteasomal degradation of I-kBa and translocate the stimulated NF-kB to the nucleus after 15 min of exposure of TNF-α [36]. NF-kB affects on the expression of genes which regulate ubiquitin proteasome pathway (UPP) and