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Revisiting the clinical usefulness of C-reactive protein in the set of cancer cachexia

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Abstract

Cancer cachexia is a highly complex multifactorial disorder that is often misdiagnosed, leading to suboptimal health outcomes. Indeed, cachexia is a concern in cancer, typifying lower response to treatment and risk of death. Thus, efforts have been made to better understand the molecular basis of this syndrome, envisioning to improve its diagnosis and management.

C-reactive protein (CRP) has been reported to be consistently increased in the circulation of patients with body wasting associated to chronic diseases. However, the role of CRP in the pathogenesis of cachexia remains elusive. Several hypotheses have been advanced but most of experimental findings support an indirect effect on the activation of muscle proteolysis, mostly through its interplay with pro-inflammatory cytokines. Herein, we overview the contribution of CRP to body wasting and its putative biomarker value for the diagnosis and follow-up of the therapeutic management of cachexia.

Abbreviations: Akt (or PKB) = protein kinase B, ALP = autophagy-lysosome pathway, AMPK = activated protein kinase, AP-1 = activator protein 1, APP = acute-phase protein, BMI = body mass index, C/EBP = CCAAT enhancer-binding proteins, CRP = C-reactive protein, FOX-O = transcription factors forkhead, Gp130 = glycoprotein 130, IGF-1 = insulin-like growth factor 1, IGF-1R = IGF-1 receptor, IkB = inhibitor of kappa B, IL = interleukin, IL-1R = IL-1 receptor, IL-6R = IL-6 receptor, IRS-1 = insulin receptor substrate 1, JAK = Janus Kinase, LC3 = microtubule-associated protein 1 light chain 3, LPC = lysophosphotidylcholine, mCRP = monomeric CRP, mRNA = messenger ribonucleic acid, mTOR = mammalian target of rapamycin, mTORC1 = mammalian target of rapamycin complex 1, MuRF1 = muscle ring finger protein 1, NF-kB = nuclear catabolic factor kappa B, NK = natural killer, pCRP = pentameric CRP, PI3K = phosphoinositide 3-kinases, PLA2 = phospholipase A2, SMAD = acronym from the fusion of *Caenorhabditis elegans* Sma genes and the *Drosophila Mad*, mothers against decapentaplegic, STAT = signal transducer and activator of transcription, Th1 = T helper cell, TNF-α = tumor necrosis factor alpha, TNFR = TNF-α receptor, UPP = ubiquitin-proteasome pathway.

Keywords: acute-phase protein, cancer, inflammation, muscle wasting

Introduction

C-reactive protein (CRP) was the first acute-phase protein to be described by Tillett and Francis in 1930, owing its name to its ability to react with C-polysaccharide of pneumococcal bacteria cell wall.[1] Since then, its clinical usefulness as marker of acute-phase response to most forms of inflammation has widely spread.[2] It is recognized that high CRP values are not diagnostic by itself, as this is commonly found in several chronic diseases, but can be very informative when integrated with other clinical data.[2–4,5] For instance, in the absence of an underlying infection, elevated circulating levels of CRP are associated with poor prognosis, advanced stages of disease[6,7] and/or to cachexia in cancer setting.[8,9] It is also associated with an increased risk of anorexia, weight loss, fatigue and pain,[10–12] which are all signs of cachexia.

Cachexia is a multifactorial syndrome defined by "an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment".[13] In the context of cancer, cachexia is usually considered when there is an involuntary weight loss higher than 5% or a body mass index (BMI) lower than 20 kg/m^2 with any degree of weight loss higher than 2%.[14] Cachectic patients also present decreased physical performance, which impairs their quality of life and the clinical outcome of disease treatment.[15] This syndrome is characterized by reduced food intake and abnormal metabolism as a result of tumor metabolism, systemic inflammation, among other effects mediated by the tumor.[14,16,17] More than half of cancer patients suffer from cachexia at the time of death.[18]

In addition to their involvement in promoting cancer cell growth, resistance to apoptosis and promotion of angiogenesis/metastasis, pro-inflammatory cytokines such as interleukin (IL)-6, IL-1 and TNF-α are the main molecular triggers of cachexia.[19] In the liver, these cytokines induce the synthesis of CRP.[19] However, the role of CRP in the modulation of body wasting, and consequently on cachexia pathogenesis, remains elusive. Herein, we explore the molecular mechanisms behind body wasting in

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cancer that are regulated by CRP and explore its putative utility for cachexia diagnosis.

Where and when CRP is produced

CRP is a plasma protein that belongs to pentraxins protein family.[20] It has 5 identical non-covalently associated protomers (206 amino acid residues) arranged symmetrically around a central pore. The protomer has a ligand binding site that consists of a pocket with 2 calcium ions bound,[21] which is also fundamental for the stability of the CRP molecule.[22] There are 2 conformational distinct forms, native pentameric CRP (pCRP) and monomeric CRP (mCRP). pCRP seems to have pro-inflammatory or anti-inflammatory properties depending on the context, while the mCRP exerts potent pro-inflammatory actions and may even amplify the inflammatory response.[23,24] Usually its pro-inflammatory action occurs in endothelial cells, endothelial progenitor cells, leukocytes and platelets.[23] The link of CRP to inflammation may result from the dissociation of pCRP into pro-inflammatory mCRP.[25] This dissociation is promoted by the binding of pCRP subunits to phosphocholine (PC) residues of lysophosphatidylcholines (LPCs) on the cell membrane. LPCs are exposed by phospholipase A2.[26] In activated monocytes, pCRP also interacts with lipid rafts on the cell surface. pCRP is encapsulated onto microvesicles where it undergoes a conformational change. In this activated form, pCRP binds to complement C1q, which forces its dissociation to mCRP.[26]

In response to most forms of tissue damage, infection, inflammation, and malignant neoplasia, hepatocytes synthetize various proteins, known as acute-phase proteins (APP, also known as positive acute-phase proteins).[20] In addition to C-reactive protein, there are other APPs, including proteinase inhibitors (eg, α1-antitrypsin, α1-antichymotrypsin) and coagulation (eg, fibrinogen, factor VIII), complement (eg, C2, C3) and transport (eg, haptoglobin, serum amyloid A) proteins. However, the only one that exhibits sensitivity and response rate comparable to CRP is the serum amyloid protein A.[3] APP synthesis is controlled by cytokines originating at the pathology site,[27] or at tumor site.[28,29] The tumor microenvironment contains innate immune cells, including macrophages, neutrophils, mast cells, myeloid derived suppressor cells, dendritic cells and natural killer (NK) cells, and also, T and B lymphocytes.[30,31] Tumor-associated macrophages are the immune cells most abundantly found in the tumor microenvironment.[30] These cells are an important source of cytokines,[32] particularly M1 macrophages that express high levels of pro-inflammatory cytokines.[33] Th1 lymphocytes are also relevant sources of pro-inflammatory cytokines.[34] Some cytokines appear to have origin in the tumor, which was reported in a large range of solid tumors.[35–37] Cancer cells overexpress the receptors for those cytokines, using them to boost tumor development and immunosuppression.[38,39] The IL-6 receptor is an example. This receptor is overexpressed in several types of cancer (eg, oral squamous cell carcinoma) and its activation leads to the upregulation of cells proliferation, differentiation and resistance to apoptosis.[31] Through the activation of several downstream effectors such as NF-kB, AP-1, STAT and SMAD, some cytokines control the immune and inflammatory environment,[30] allowing the tumor to grow progressively without the immunological constraints.[40] This immunosuppressive microenvironment is also favored by different features of tumor cells' metabolism.[41,42] Cancer cells switch from mitochondrial oxidative phosphorylation to aerobic glycolysis, a metabolic reprogramming known as "Warburg effect".[41,43] The resultant local acidity and the hypoxia that characterizes solid tumors with rapid tumor growth and aberrant vasculature formation have profound effects on both innate and adaptive immune cells.[44] For instance, T cell differentiation and function, and NK cell cytotoxic properties are impaired by insufficient oxygen supply.[44]

The most well characterized pro-inflammatory cytokine that regulates CRP synthesis is interleukin (IL)-6, and to a lesser extent IL-1β.[45] This regulation occurs via recruitment and activation of family members C/EBP (C/EBPβ and C/EBPα), NF-kB and STAT3 pathways.[45–47] STAT3 and Rel proteins bind to the proximal CRP promoter, with subsequent interactions resulting in increased C/EBP binding, thereby facilitating maximal CRP overexpression.[48] Once synthesized, CRP is rapidly secreted by liver cells (Fig. 1).[49] An increase in CRP circulating levels is not immediately noticed, being detected after 6 to 8 hours, peaking at 24 to 48 hours. Although CRP is mainly synthesized in the liver, its mRNA was also detected in respiratory tract epithelial cells, T-lymphocytes,[50] adipose tissues, epithelial cells of renal cortical tubules, and in smooth muscle cells and macrophages from atherosclerotic plaques.[51]

CRP synthesis is stimulated by several factors such as aging, increased blood pressure, smoking, coffee and alcohol consumption, decreased physical activity, high triglyceride levels, insulin, high protein diet, chronic tiredness and sleep disturbances, and depression.[52] The mechanisms involved in age-related increase of chronic inflammation are not fully understood. It has been proposed that the highest levels of CRP, and other inflammatory markers, are related to increased volume of adipose tissue (especially visceral), decline of sex hormones, and increased oxidative damage, common situations in the elderly individuals.[53] In addition, aging usually results in immunosenescence, a process characterized by the functional decline of the immune system, resulting in increased susceptibility to infectious diseases and prevalence of non-communicable diseases.[54] However, age-related inflammatory status might be modulated by lifestyle. For instance, the decrease of TNF-α and IL-6 circulating levels has been associated with an active lifestyle.[55] Consequently, diminished CRP production and secretion is observed.[56] Physical activity also induces the increase of circulating anti-inflammatory cytokines, such as the IL-1 receptor antagonist and IL-10, which hamper the production of CRP.[54,57]

C-reactive protein in cancer cachexia

Epidemiologic studies highlight an association between elevated circulating CRP levels, measured by high-sensitivity assays, and the risk of certain types of cancer.[58–67] For example, elevated concentrations of CRP have been positively associated with epithelial cancers such as liver, lung, colorectal, endometrial and breast.[63–67] Moreover, a positive association between CRP and a poor prognosis of cancer was reported, with an evident relationship between its levels and disease prognosis.[6] Comparing cancer types, the highest mCRP values appear to be detected in esophagus, rectum, colon, bladder and pancreas cancer patients.[6] In addition, males with advanced cancers present higher levels of CRP than females, which was associated with more weight loss and shorter survival.[68] Despite the prognostic value of CRP for advanced cancers,[6,7] the molecular basis behind this association are not known.

Up to 50% to 80% of cancer patients exhibit cachexia at advanced stages of disease.[69] The prevalence of this syndrome reaches 86% in the last 1 to 2 weeks of life.[70] Thus, the increase in

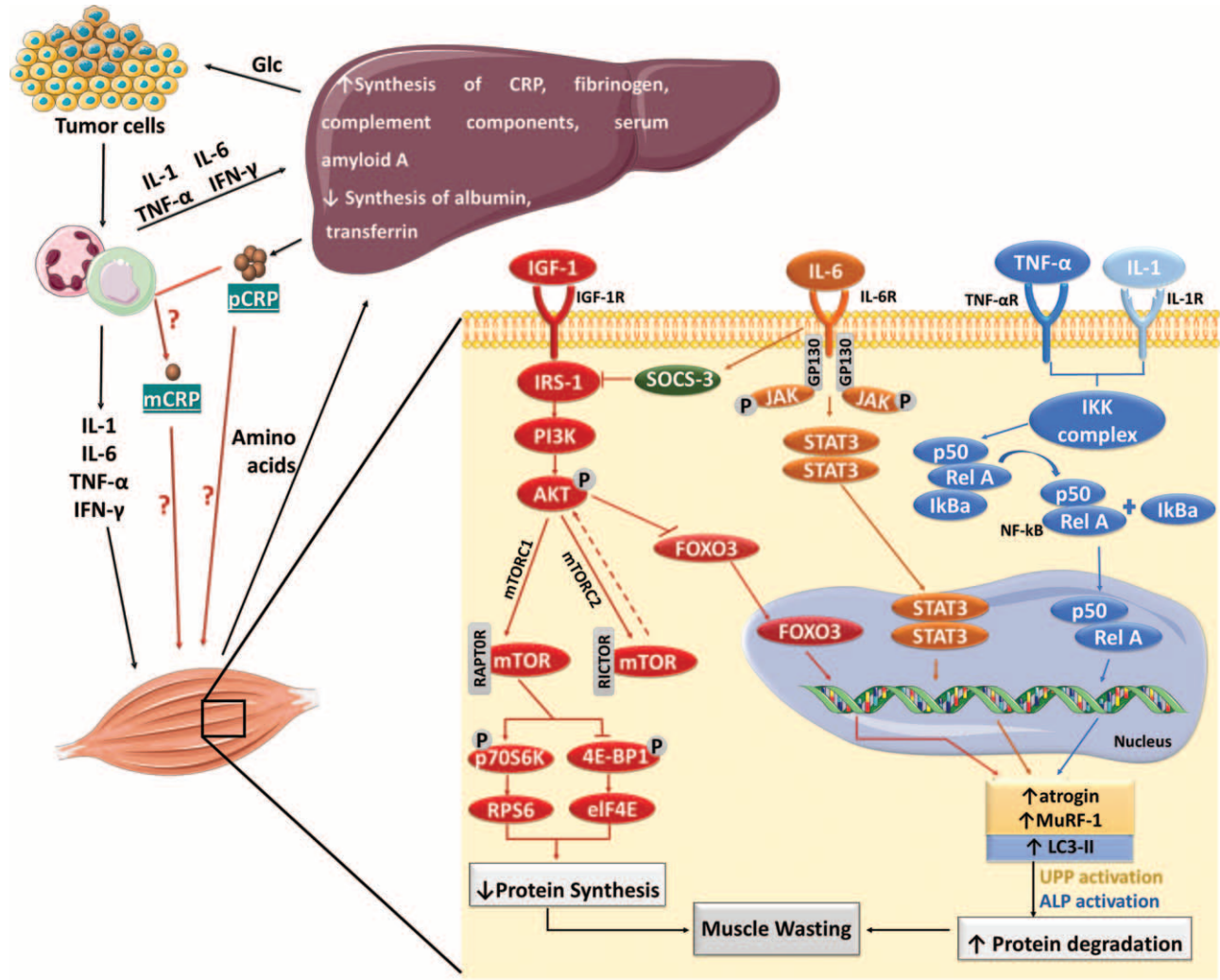

Figure 1. An overview of the signaling pathways behind the role of CRP in cancer-induced muscle wasting. Pro-inflammatory cytokines drive the synthesis of CRP by the liver. The pro-inflammatory properties CRP are associated to the spread of pro-inflammatory cytokines synthesis, which act on skeletal muscle, activating specific signaling pathways such as STAT and NF-kB pathways. These pathways activate the expression of E3 ligases from the UPP. Concomitantly, the Akt/mTOR pathway is downregulated. Thus, FOXO3 phosphorylation is suppressed, allowing its translocation to the nucleus where it regulates the expression of atrogin and MuRF1. The direct effect of CRP was reported and seems to occur through the inhibition of Akt signaling; however, the mechanisms involved are not known (figure produced using Servier Medical Art). Akt = protein kinase B, ALP = autophagy-lysosome pathway, FOXO3 = forkhead box O3, Glc = glucose, gp130 = glycoprotein 130, IGF-1 = insulin-like growth factor 1, IGF-1R = IGF-1 receptor, IkB = inhibitor of kappa B, IL = interleukin, IL-1R = IL-1 receptor, IL-6R = IL-6 receptor, IRS-1 = insulin receptor substrate 1, JAK = Janus Kinase, LC3 = microtubule-associated protein 1 light chain 3, mCRP = monomeric CRP, pCRP = pentameric CRP, PI3K = phosphoinositide 3-kinases, STAT3 = activator of transcription 3, TNF-αR = TNF-α receptor, UPP = ubiquitin-proteasome pathway.

systemic inflammation given by circulating levels of APPs such as CRP seems to be associated to muscle mass loss[9] and elevated CRP levels were shown to be an early predictor of severe lean tissue loss.[6,71] Although not yet fully understood, some hypotheses have been raised to mechanistically explain this association. To the best of our knowledge, no receptors for CRP have been reported in skeletal muscle. The most widely recognized inflammatory-related triggers of muscle decline in cancer are the pro-inflammatory cytokines (Fig. 1).[72] Nevertheless, some redundancy in their participation in prompting muscle wasting has been noticed in literature. Several issues seem to contribute to this lack of consistency, such as cancer type.[8,73]

It has been argued that the cytokines that stimulate the synthesis of CRP in hepatocytes also act on skeletal muscle.[74] By activating neutrophils and monocytes to secrete IL-6, IL-1β and TNF-α, CRP indirectly promotes muscle wasting.[24] Pro-inflammatory cytokines such as IL-6 act on JAK/STAT receptors in skeletal muscle.[75,76] The activation of STAT3, by phosphorylation, leads to the spontaneous dimerization of this transcription factor. This pathway ends with phospho-STAT3 being translocated to the nucleus, where the dimers bind to the consensus sequences in the promoter regions of the target genes (Fig. 1).[77] Consequently, the expression of atrogin and MuRF1 increases. These E3 ligases from the ubiquitin-proteasome pathway (UPP) participate in the breakdown of muscle proteins.[78] The nuclear catabolic factor kappa B (NF-kB) may also be activated by IL-1 and TNF-α.[79,80] This transcription factor has an important role in the regulation of the UPP.[81] Other proteolytic pathways intervene in muscle wasting such as the autophagic-lysosomal process. This proteolytic pathway seems to be required to energetically sustain tumor growth.[82] Pro-inflammatory cytokines also down-regulates muscle anabolic

capacity, through the modulation of IGF-1 dependent signaling pathway (Fig. 1).[83] All these molecular events driven by inflammation lead to muscle wasting.[84] However, muscle fibers are not affected in the same way. Several studies suggest that type II fibers are the most vulnerable to cachexia, possibly because they are preferential targets of pro-inflammatory cytokines.[85–88] Indeed, increased inflammatory signaling leads to changes in muscle contractile phenotype.[89] In tumor-bearing mice, muscle wasting was related with a slow-to-fast transition,[90] a phenotype characterized by decreased oxidative metabolism and mitochondrial density.[89] However, very few studies have explored muscle phenotype remodeling in cachexia and, to the best of our knowledge, no studies have compared the distribution of cytokine receptors among distinct fiber types.

CRP has been implicated in the regulation of muscle cells' proliferative and metabolic activities. Myogenic cells exposed to serum from elderly women with elevated CRP levels showed reduced proliferative rates.[91] The proliferative rate of other cell types, such as endothelial cells was also reported to be affected by serum with increased CRP content.[92] The molecular mechanisms behind this effect are not understood but seems to be indirect, through IL-6. This pro-inflammatory cytokine promotes the downregulation of the Akt/mTOR pathway in muscle fibers (Fig. 1).[75] However, Wåhlin-Larsson et al[93] reported a CRP-mediated reduction in Akt phosphorylation based on experimental observations retrieved from myotubules exposed to CRP added to culture medium (at a concentration of 50 μg/mL). Other molecular players were reported to be affected by CRP, such as ribosomal protein S6. The phosphorylation levels of this critical component of the 40S ribosomal subunit was also shown to be reduced. In opposition, an increase in the phosphorylated form of Raptor Ser792 was observed.[93] Raptor is a direct substrate of AMPK and a mTOR-binding-partner, linked to the inhibition of mTORC1 (Fig. 1).[94] To the best of our knowledge, there are no *in vivo* studies reporting a direct role of CRP in muscle remodeling.

If by one side inflammation seems to trigger muscle wasting, then muscle wasting seems to support the inflammatory status[95] and also to support tumor's metabolic needs.[70,96] For instance, glutamine is released by skeletal muscle in order to provide energetic substrate and precursors to be used in nucleic acid synthesis for rapidly dividing cells, such as tumor and immune cells.[96] Alanine is other example of an amino acid exported in large quantities from skeletal muscle and used to support liver gluconeogenesis, giving glucose for tumor cells.[95] Amino acids secreted by wasted skeletal muscle also support APP synthesis by the liver (Fig. 1).[95,96] Thus, the interplay between liver, muscle fibers, immune and tumor cells seem to be critical in feeding the wasting phenotype characteristic of advanced stages of cancer.

Limitations in the application of CRP as a biomarker of cancer cachexia

Detecting cachexia at its early stages has been a major goal in the care of cancer patients. Several putative biomarkers derived from different body compartments have been advanced, such as myostatin, ghrelin and pro-inflammatory cytokines.[97,98] From these, pro-inflammatory cytokines have been the preferential targets of intensive research in the set of cancer cachexia; however, cytokines profile vary with tumor type and stage.[99] Since it does not seem to be modulated by these variables, CRP is a promising candidate marker of cachexia in the set of cancer.[6] Still, there are some limitations to be considered in the interpretation of CRP values for diagnosis. The specificity and cutoff values are probably the main problems.[7] For instance, an underlying infection should be ruled out when assessing the diagnosis value of CRP in the set of cancer cachexia.[100] The most commonly used cutoff point to define cachexia appears to be CRP concentration higher than 10 mg/L.[6] However, a cutoff higher than 25 mg/L was also reported.[100] Shrotriya et al[7] reviewed 271 studies and in 92 of them, the cutoff value of CRP for cachexia diagnosis was set at 10 mg/L. However, in the remaining analyzed studies the reported cutoffs varied from values higher than 2 mg/L to values higher than 50 mg/L. Such discrepancies may be due to the use of distinct laboratory methodologies for CRP assessment.[101] Moreover, CRP synthesis is modulated not only by several clinical conditions[102] but also by lifestyle,[103] which challenge the definition of a unique cutoff value for all cancer patients' population. Eventually, more than a single CRP cutoff value should be considered, depending on the screened population.

Conclusions

CRP is a highly sensitive marker of inflammation to be considered in the diagnosis of cancer cachexia. Indeed, the levels of this acute-phase protein reflect the interplay between inflammation and muscle decline in the set of noncommunicable diseases such as cancer. However, the application of CRP in the clinical assessment of cancer cachexia has been hampered by several issues, such as its lack of specificity for cachexia and the poor comprehension of its role in the activation of muscle wasting. Most of the studies suggest an indirect effect, through pro-inflammatory cytokines with only one study suggesting a direct role. Moreover, CRP levels are very responsive to lifestyle and several pathophysiological conditions. Thus, the identification of cutoff values for CRP values is needed and should consider the heterogeneity of cancer patients' clinical profile. The definition of a standard laboratory method will help to define these cutoff values. Future studies should also explore the mechanistic association of CRP with muscle decline. With such information, CRP might be proposed as a relevant marker for the early diagnosis of cachexia and the follow-up of anti-cachexia therapeutic approaches.

Conflicts of interest

The authors declare no conflicts of interest.

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