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Review

Muscle wasting in cancer☆

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ABSTRACT

Skeletal muscle loss appears to be the most significant clinical event in cancer cachexia and is associated with a poor outcome. With regard to such muscle loss, despite extensive study in a range of models, there is ongoing debate as to whether a reduction in protein synthesis, an increase in degradation or a combination of both is the more relevant. Each model differs in terms of key mediators and the pathways activated in skeletal muscle. Certain models do suggest that decreased synthesis accompanied by enhanced protein degradation via the ubiquitin proteasome pathway (UPP) is important. Murine models tend to involve rapid development of cachexia and may represent more acute muscle atrophy rather than the chronic wasting observed in humans. There is a paucity of human data both at a basic descriptive level and at a molecular/mechanism level. Progress in treating the human form of cancer cachexia can only move forwards through carefully designed large randomised controlled clinical trials of specific therapies with validated biomarkers of relevance to underlying mechanisms.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

Abbreviations: ACTRIIB, activin receptor type-2B; APC, adenomatosis polyposis coli; APPR, acute phase protein response; ARC, arcuate nucleus; ATP, adenosine-5′-triphosphate; C-26, colon-26 adenocarcinoma mouse model; CHO, Chinese hamster ovary; COPD, chronic obstructive pulmonary disease; CRPc, reactive protein; CSA, cross sectional area; DGC, dystrophin glycoprotein complex; DM, diabetes mellitus; DNA, deoxyribonucleic acid; EDL, extensor digitorum longus; EIF3F, eukaryotic translation initiation factor 3 subunit F; F-bxo40, F-box protein 40; FCSA, fibre cross sectional area; FOXO, forkhead box class O transcription factor; ICU, intensive care unit; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; IRS, insulin receptor substrate; JAK, Janus associated kinase; LBM, lean body mass; LLC, Lewis lung carcinoma; MA, megestrol acetate; mAb, monoclonal antibody; MAC16, murine adenocarcinoma 16 mouse model; MAFbx, muscle-specific F-box (also known as atrogin-1); MAPK, mitogen activated kinase; MCR, melanocortin receptor; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; MSH, melanocyte-stimulating hormone; mTOR, mammalian target of rapamycin; MURF-1, muscle-specific RING finger-1; MyHC, myosin heavy chain; NFκB, nuclear factor-κβ; NPY, neuropeptide Y; NSCLC, non-small cell lung cancer; PBMC, peripheral blood mononuclear cell; PI3K, phosphatidylinositol 3-kinase; POMC, pro-opiomelanocortin; QoL, quality of life; RNA, ribonucleic acid; STAT, signal transducer and activator of transcription; TA, tibialis anterior; TAM, tumour-associated macrophage; TGF, transforming growth factor; T_h, T helper; TNF, tumour necrosis factor; TWEAK, tumour necrosis factor-like weak inducer of apoptosis; Ub, ubiquitin; UPP, ubiquitin-proteasome pathway.

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1. Introduction

Weight loss in cancer patients is associated with excess morbidity and mortality (Rennie, 2009; Brandt and Pedersen, 2010). Cachexia affects the majority of patients with advanced cancer and is associated with a reduction in treatment tolerance, response to therapy, quality of life and duration of survival. Cancer cachexia has recently been defined as a multifactorial syndrome characterised 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 (Fearon et al., 2011). Although there is depletion of both adipose tissue and lean body mass, it is skeletal muscle loss that has the greatest impact on patients' function and quality of life and is clearly associated with a poor outcome (Tan et al., 2009; Fearon et al., 2011; Miller et al., 2012).

2. Heterogeneity

Heterogeneity both in clinical and animal models is one of the key issues that has impaired research into cancer cachexia. Cachexia is not a single phenomenon but evolves through a spectrum of pre cachexia, cachexia, and refractory cachexia (Fearon et al., 2011). The incidence and severity of cachexia can vary according to tumour type, site, and mass (Dewys et al., 1980). Equally, the contribution of reduced food intake versus abnormal metabolism can vary considerably (Knox et al., 1983). The components of such abnormal metabolism also vary, and within the same model/individual can evolve with time such that hypermetabolism (Zylicz et al., 1990) or activation of proteolytic pathways (Khal et al., 2005a,b) occurs during the early phase of cachexia but not during a more advanced phase. In humans the cause of such heterogeneity relates not only to the clinical status of the patient and specific effects of the tumour (e.g. causing bowel obstruction, tissue destruction or concomitant infection) but also to co-existing morbidities (e.g. heart failure, chronic renal failure, or chronic obstructive pulmonary disease), age related sarcopenia and the possibility of a genetic predisposition to develop cachexia (Fig. 1).

There are numerous animal models of cancer cachexia. A recent review concluded that for research into cancer cachexia where there is little evidence of systemic inflammation, the murine adenocarcinoma 16 mouse (MAC-16) and XK1 murine tumour models are useful (Bennani-Baiti and Walsh, 2011). Weight loss in mice bearing the MAC-16 tumour appears to be independent of reduced food intake or inflammation (Bennani-Baiti and Walsh, 2011). In contrast the XK1 model demonstrates reduced food intake. All other models induce a host inflammatory response. In the Walker 256 and MCG – 101 models tumour growth is extremely rapid resulting in a tumour mass exceeding 10% of host body weight in a matter of days (Bennani-Baiti and Walsh, 2011). This highlights the problems with the translational value of relatively acute onset cancer cachexia seen in murine models compared with humans where a cancer may spread over a period of months or years (with similar time scale for the evolution of cachexia). One of the most popular models at present is a particular clone of the colon-26 adenocarcinoma (C26) tumour in mice. This is thought to be a mainly IL-6 dependant model of cachexia (Strassmann et al., 1992). Whether, in fact, this can be considered as representative of the majority of cancer patients remains highly speculative.

3. Skeletal muscle morphology in cancer associated myopenia: murine models

Skeletal muscle is composed of muscle fibres which are classified according to their speed of contraction and predominant type of energy metabolism. Muscle fibres can be classified as type I, slow-twitch and type II, fast-twitch fibres based on their predominant myosin heavy chain (MyHC) isoform content. Generally, type I and type IIa fibres utilise oxidative phosphorylation as their energy source, whereas type II*x* and IIb fibres harness anaerobic metabolism to generate ATP (Schiaffino and Reggiani, 1996; Berchtold et al., 2000). Both the percentage and structural morphology of the fibre type will determine the phenotypic capacity and functional performance of any given muscle. Environmental factors in both health and disease have a direct impact on muscles leading to changes in fibre type and morphology which lead to changes in muscle functionality; such processes include ageing, exercise, diabetes, disuse atrophy, chronic heart failure, and cachexia (Lipkin et al., 1988; Mancini et al., 1989; Sullivan et al., 1990; Drexler et al., 1992; Belardinelli et al., 1995; Short and Nair, 2001; Basu et al., 2002; Marx et al., 2002; Short et al., 2004; Schmitt et al., 2007; Weber et al., 2007; Eley et al., 2008; Harber et al., 2009; Weber et al., 2009). The change, preservation or loss of fibres may influence clinical symptoms and there is some evidence that fibre

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