Fn14: a new player in cancer-induced cachexia

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Purpose of review
Although cancer cachexia is a very significant condition that is present in up to 80% of cancer cases, the cause of the condition has remained a puzzle. Cancer cachexia is a condition which is mainly characterised by muscle wasting, mobilization of fat reserves, and overall metabolic disturbance. This review aims to highlight some of the recent findings in cancer cachexia research.

Recent research
It has been recently demonstrated that the expression of a single receptor, *fibroblast growth factor-inducible 14*, on a tumour can initiate cachexia and that this can be completely ablated by treatment with an antibody against this receptor. Also recently described was the role of parathyroid hormone receptor-binding proteins in causing cachexia through a mechanism where white adipose tissue is replaced with brown adipose tissue. In parallel, work done in drosophila suggests that the impaired insulin signalling is a direct cause of cancer cachexia through the release of an insulin growth factor binding protein that inhibits insulin and *insulin-like growth factor 1* signalling.

Summary
Successful therapies are urgently needed to combat cancer cachexia in the clinic. Recent research is making progress toward discovering the underlying molecular causes of the condition, which could lead to new therapeutic approaches and in the future contribute to more positive clinical outcomes for cancer sufferers.

Keywords
brown-adipose tissue, cachexia, cancer, insulin signalling, muscle-wasting, tumour-tissue communications

INTRODUCTION

Cachexia

Cachexia is frequently present in the terminal stages of many chronic illnesses including cancer and is the condition whereby a patient suffers from the loss of skeletal muscle mass, adipose tissue mass, and overall metabolic imbalance [1,2]. The presence of cachexia not only reduces patient response to antineoplastic treatments and increases the risk of postoperative complications, but also dramatically reduces a patient's quality of life. There are no effective treatments for this condition and currently, no drugs have been approved by the Food and Drug Administration for the treatment of cancer cachexia.

Although traditionally cancer cachexia has been thought of simply as part of cancer progression, it is becoming more widely accepted as a definable and potentially separate targetable condition. There is good recent progress in defining the molecular mechanisms and it is also becoming clearer that there are a variety of mechanisms at play, which are involved in establishing this condition and may depend on a variety of initiating factors. Downstream of the initiating factors is inflammation and the subsequent release of inflammatory cytokines, which is strongly associated with cachexia. Some of the inflammatory cytokines that have been implicated include tumour necrosis factor, *interleukin (IL-1), IL-6* and *interferon (IFN)*-γ [1]. A number of biologics against these cytokines are in development or in clinical trial whereas some trial results demonstrate a certain degree of efficacy others have been less fruitful.

Insulin signalling

The perturbed metabolism that is associated with cancer has been regarded as a consequence of

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KEY POINTS

- Cancer cachexia is one of the major complications of cancer for which there is no current therapy.
- Fibroblast growth factor-inducible 14 (Fn14) has been shown to induce cancer cachexia in mouse models and this could be blocked by specific Fn14 antibodies.
- Tumour-induced cachexia caused by *Fn14* occurs in a TWEAK-independent manner.
- Involvement of the parathyroid hormone receptor in adipose tissue metabolism has been recently described in the formation of cachexia.
- Impaired insulin signalling was recently reported in *Drosophila* to directly cause cancer cachexia through tumour released factors such as Imaginal morphogenesis protein-Late 2 (ImpL2).

inflammation, although recent work with *Drosophila*, suggests that the impaired insulin signalling is a direct cause of cancer cachexia through the release of tumour factors such as ImpL2, an insulin growth factor binding protein, that inhibits insulin and insulin-like growth factor 1 (IGF1) signalling [3▪,4▪]. Insulin resistance is common and may contribute to skeletal muscle wasting in mouse models of cancer cachexia through anabolic signalling, although low dose insulin had no effect on muscle loss in cachexia [5].

Fn14 as a player in tumour-induced cachexia

Fn14 is the receptor for TWEAK (Tumour Necrosis Factor Superfamily member 12) and this signalling pathway has been shown to play multiple roles in the process of wound repair, promotion of angiogenesis, proliferation, migration, apoptosis, and inflammation [6▪▪] and consistent with this, *Fn14* expression is strongly increased following wounding. In addition, *Fn14* expression is increased in solid tumours and given this involvement of TWEAK/Fn14 signalling in the processes that feature during carcinogenesis, targeting this pathway with monoclonal antibodies has proven beneficial in inhibiting tumour growth. TWEAK activates both canonical and noncanonical nuclear factor-κB signalling pathways [7▪], increases expression of genes associated with inflammation and fibrosis in myotubes, and promotes myofibril atrophy. In-vivo studies using *TWEAK* transgenic and *TWEAK* or *Fn14* knockout mice support the idea that regulating myogenesis and muscle repair are physiological functions of the TWEAK/Fn14 signalling axis [7▪]. For example, transgenic overexpression of TWEAK in skeletal muscle leads to muscle atrophy in mice whereas TWEAK-deficient mice have improved regeneration of skeletal muscle after injury.

Recently, it was shown that tumour located Fn14 [tumour necrosis factor receptor superfamily member 12A (*TNFRSF12A*)] caused cachexia in several mouse models of cachexia and this could be blocked by specific *Fn14* monoclonal antibodies [6▪▪]. Although TWEAK and Fn14 have been reported to work together in muscle and tumour biology, surprisingly, *Fn14* caused muscle wasting and adipose tissue degradation in mouse models of cachexia without the participation of TWEAK, as demonstrated by cachexia symptoms as severe in TWEAK knockout mice as in wild-type mice and antibodies specific for blocking TWEAK also had no effect on the cachexia. Ligand-independent signalling through Fn14 has previously been suggested yet until this finding, the only evidence of this being a possibility was in in-vitro overexpression studies [6▪▪]. It was also found that the cachectic signal originating from the tumour was as severe in *Fn14* knockout mice as in wild type mice, suggesting a lack of *Fn14* involvement in distal tissue such as muscle and adipose tissue. Although TWEAK itself has been implicated in the induction of atrophy pathways by directly acting on muscle *Fn14*, in these cancer models of cachexia where TWEAK is not a player, the release of soluble factors as a direct result of tumour *Fn14* action and microenvironment, are likely to be responsible for causing the cachectic symptoms in the peripheral tissues.

TGF-β family members

In mouse models, the release from tumours of transforming growth factor (TGF)-β family members such as activin A, myostatin, and growth differentiation factor 15 have previously been reported to cause cachexia. Experiments using antibodies against myostatin have demonstrated efficacy in reducing cachexia in mouse cancer models and a humanized antibody to myostatin is currently in trial in humans [8]. The receptor for these TGF-β molecules, activin receptor IIb (ActRIIb) on muscle cells, has been tested as a soluble decoy receptor during tumour-induced cachexia and was able to block the loss of muscle mass [8]. Unfortunately, treatment with a decoy ActRIIb in clinical trials with healthy adults and boys with Duchenne muscular dystrophy were stopped because of treatment-related bleeding issues and so have not been pursued for cachexia treatment, highlighting the numerous other roles these target molecules play within the body. A modified version that has reduced activin

binding has, however, showed encouraging activity in promoting haematopoiesis in mice [9].

Parathyroid hormone receptor-binding proteins

There is an emerging literature that suggests that a key metabolic change in cancer cachexia is the 'browning' of fat, where white adipose tissue becomes infiltrated with brown adipose cells (reviewed in [10]). The thermogenic activity of these cells increases the energy expenditure in rodent cells leading to fat loss. The infiltration of brown fat cells into white fat adipose deposits has been shown to be responsible for cancer cachexia in rodent models [11▪,12]. In rodent models of kidney failure induced cachexia and cancer cachexia, it was shown that tumour derived parathyroid hormone-related protein and parathyroid hormone both of which utilize the parathyroid hormone receptor (*PTHR*), caused cachexia and this was ablated by the knockout of *PTHR* [13▪▪]. The tumour derived parathyroid hormone-related protein was responsible for the browning of adipose tissue and muscle wasting, both of which was ablated by the loss of *PTHR*.

In muscle tissue, various proteins involved in muscle degradation such as the ubiquitin ligases muscle RING finger 1 (MuRF1) and atrogin-1 are highly induced in atrophying muscles, although the inactivation of their genes only provides a partial sparing of muscle loss, suggesting that other mechanisms play an important role [13▪▪]. Indeed, the deubiquitination enzyme, ubiquitin specific peptidase 19 (*USP19*) is increased in many catabolic conditions and *USP19* knockout mice were significantly protected from muscle loss in several models of muscle wasting. Concomitantly, the MuRF1 and atrogin-1 ubiquitin ligases were decreased in the catabolic knockout mice, as well as proteins involved in autophagy, suggesting that these proteins play a role in muscle degradation in cachexia [13▪▪].

CONCLUSION

A key question in developing a cancer cachexia therapy is whether there is a single initiating molecular event or a number of different events that cause cachexia in different types of cancers. Similarly, there are many different forms of non-cancer cachexia ranging from cachexia associated with chronic conditions such as kidney failure and multiple sclerosis to sarcopenia, a form of cachexia associated with aging. It remains to be seen whether each of these conditions has a similar underlying mechanism or whether each has a unique mechanism requiring a unique therapeutic solution. The recent identification of *Fn14* as a player in cancer cachexia could in the future lead to new therapeutic approaches and contribute to more positive clinical outcomes for cancer sufferers.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Petruzzelli M, Wagner EF. Mechanisms of metabolic dysfunction in cancer associated cachexia. Genes Dev 2016; 30:489–501.
2. Lok C. Cachexia: the last illness. Nature 2015; 528:182–183.
3. ▪ Kwon Y, Song W, Droujinine IA, *et al.* Systemic organ wasting induced by localized expression of the secreted insulin/IGF antagonist ImpL2. Dev Cell 2015; 33:36–46.

The study shows that the stimulation of the fruit fly insulin growth factor binding protein, Imp1L2 inhibits insulin and *IGF1* signalling causes systemic muscle wasting and organ wasting, including fat bodies.

4. ▪ Figueroa-Clarevega A, Bilder D. Malignant Drosophila tumors interrupt insulin signaling to induce cachexia-like wasting. Dev Cell 2015; 33:47–55.

The study shows that the transplantation of tumours into adult flies caused wasting of fat and muscle through a mechanism of insulin downregulation in peripheral tissues.

5. Wagner EF, Petruzzelli M. Cancer metabolism: a waste of insulin interference. Nature 2015; 521:430–431.
6. ▪▪ Johnston AJ, Murphy KT, Jenkinson L, *et al.* Targeting of *Fn14* prevents cancer-induced cachexia and prolongs survival. Cell 2015; 162:1365–1378.

The study shows that the expression of the tumour necrosis factor receptor family member, *Fn14*, in tumours causes cachexia and this can be blocked and reversed by treatment of mice with anti-*Fn14* monoclonal antibodies.

7. ▪ Tajrishi MM, Zheng TS, Burkly LC, *et al.* The TWEAK-*Fn14* pathway: a potent regulator of skeletal muscle biology in health and disease. Cytokine Growth Factor Rev 2014; 25:215–225.

This review summarises what is known about the role of the Fn14/Tweak pathway in skeletal muscle regulation and during muscle atrophy.

8. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov 2015; 14:58–74.
9. Suragani RN, Cawley SM, Li R, *et al.* Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine beta-thalassemia. Blood 2014; 123:3864–3872.
10. Tsoli M, Swarbrick MM, Robertson GR. Lipolytic and thermogenic depletion of adipose tissue in cancer cachexia. Semin Cell Dev Biol 2015. (In press).
11. ▪ Kir S, White JP, Kleiner S, *et al.* Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. Nature 2014; 513:100–104.

The work shows that a parathyroid hormone-related peptide derived from tumour cells causes adipose tissue browning and cachexia.

12. Petruzzelli M, Schweiger M, Schreiber R, *et al.* A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. Cell Metab 2014; 20:433–447.
13. ▪▪ Kir S, Komaba H, Garcia AP, *et al.* PTH/PTHrP receptor mediates cachexia in models of kidney failure and cancer. Cell Metab 2015; 23:315–323.

The work illustrates the importance of adipose tissue metabolism in the formation of cachexia through the parathyroid hormone receptor. Fat tissue-specific knockout of the receptor not only affects the browning of adipose tissue but also muscle wasting.