British Journal of Nutrition (2005), **93**, 761–763
DOI: 10.1079/BJN20051459

Invited commentary

Insight into the growth hormone–insulin-like growth factor-I axis in cancer cachexia

Cachexia, a catabolic state characterised by progressive weight loss with depletion of skeletal muscle and adipose tissue, is a debilitating syndrome that occurs in many chronic diseases, such as cancer, sepsis, AIDS and congestive heart failure. Cachexia affects most patients with advanced cancer, being more common and severe in patients with cancers of the gastrointestinal tract and lung (Dewys *et al*. 1980; Fearon & Moses, 2002). Progressive cachexia predicts an overall poor prognosis and prevents effective therapeutic interventions for cancer. Cachexia increases morbidity and mortality in cancer patients, and has been estimated to account for about 20 % of cancer deaths. Despite its significant clinical importance, the mechanisms of cancer cachexia remain to be fully understood. Treatments designed to ameliorate cancer-induced weight loss, such as nutritional supplementation, have failed to reverse the catabolic process, particularly the loss of muscle mass (Tisdale, 2002).

Cancer cachexia is considered to be multifactorial, resulting from an imbalance between catabolic and anabolic processes. This has led to a question of which factors cause the metabolic disturbances. Several lines of evidence suggest that increases in cachectic mediators such as pro-inflammatory cytokines, glucocorticoids and tumour-derived catabolic factors, as well as changes in production of the major anabolic hormones including insulin, growth hormone (GH) and insulin-like growth factor-I (IGF-I), may contribute (Schaur *et al.* 1979; Todorov *et al.* 1996; Bing *et al.* 2001; Crown *et al.* 2002; Argiles *et al.* 2003). The paper by Huang *et al.* (2005) in the present issue of the *British Journal of Nutrition* has reported disturbances in the GH–IGF-I axis in patients with cancer cachexia.

There is growing interest in the role of the GH–IGF-I axis in the aetiology of cachexia, largely because GH and IGF-I have potent anabolic effects with therapeutic potential. GH, released from the pituitary gland in a pulsatile manner, promotes growth directly in selected target tissues or indirectly through activation of the somatomedins and in particular IGF-I (Cicoira *et al.* 2003). IGF-I, with a primary structure similar to insulin (Rinderknecht & Humbel, 1978), is mainly produced by the liver, which serves as a major source of the circulating pool, although synthesis of IGF-I occurs in most tissues. Circulating IGF-I is bound to insulin-like growth factor-binding proteins (IGFBP) which regulate its bioactivity; IGFBP-3 binds 85 % of circulating IGF-I thereby acting as a biological storage system (Durai *et al.* 2005). IGF-I mediates the effect of GH on developmental growth, stimulates cell proliferation and differentiation, and regulates metabolism (Boulware *et al.* 1992; Jones & Clemmons, 1995). In particular, IGF-I has been demonstrated to enhance protein synthesis and to decrease protein degradation (Hussain *et al.* 1994; Fryburg *et al.* 1995).

The primary regulator of IGF-I synthesis and secretion in hepatocytes is GH. Gene expression of IGF-I in the liver has been shown to be down-regulated in GH-deficient mice whilst markedly increased in transgenic mice over-expressing GH (Iida *et al.* 2004). Changes in plasma IGF-I mirror changes in GH secretion that occur throughout the life span. In children with GH deficiency, serum IGF-I levels are low but increase appropriately with GH replacement therapy (Dean *et al.* 1982). In addition to GH, insulin has been shown to increase the bioactivity of IGF-I by enhancing its synthesis and decreasing some of its binding proteins (Kaaks & Lukanova, 2001). Plasma IGF-I concentrations are low in children with insulin-dependent diabetes mellitus, which can be restored to the normal range with insulin replacement (Bereket *et al.* 1995). Nutrition is another important regulator of plasma IGF-I. Fasting leads to a substantial decrease in plasma IGF-I in man (Clemmons *et al.* 1981), while chronic malnutrition induced by either energy or protein deprivation in rats leads to reduction in liver IGF-I mRNA and serum IGF-I levels (Oster *et al.* 1995). Catabolic conditions such as renal failure, hepatic failure and inflammatory bowel disease also result in major decreases in IGF-I (Cohen *et al.* 2000), but the extent to which this is a consequence of reduced food intake or the inflammatory response is not known.

Enhanced catabolism and severe malnutrition are associated with a condition referred to as acquired GH resistance, which can be defined by elevated circulating GH but decreased IGF-I levels that may be associated with changes of IGFBP. Although it is not clear whether IGF-I falls due to reduced synthesis or increased clearance, decreased circulating IGF-I is suggested to result in an up-regulation of GH probably by loss of negative feedback (Jenkins & Ross, 1998). In addition, the changes in the GH–IGF-I axis may reflect an attempt to correct the catabolic situation by reducing IGF-I in the circulation and increasing its bioavailability to the tissues (Cwyfan Hughes *et al.* 1992; Skjaerbaek *et al.* 1998). None the less, treatment targeted to restore IGF-I levels by administration of IGF-I or GH has been demonstrated to lessen the extent of wasting. For example, treatment with IGF-I has been shown to protect against protein loss during cachectic states in experimental models of starvation (O'Sullivan *et al.* 1989), diabetes (Tomas *et al.* 1991) and ischaemic acute renal failure (Ding *et al.* 1993). Burn patients who receive IGF-I exhibit a decline in protein oxidation (Cioffi *et al.* 1994), and in patients with liver cirrhosis, GH treatment leads to increases in circulating IGF-I and IGFBP-3 levels and improved nitrogen balance (Donaghy *et al.* 1997). Acquired GH resistance has been reported in several catabolic states, including infection (sepsis, AIDS), organ failure (congestive heart failure, liver cirrhosis) and insulin-dependent diabetes mellitus (Anker

et al. 2001). Changes in the GH–IGF-I axis in these wasting states would suggest that the neuroendocrine alterations (in particular the low levels of IGF-I) might represent a common pathophysiological mechanism that leads to the catabolic conditions.

Despite the frequent occurrence of wasting in cancer patients, studies of the GH–IGF-I axis in the pathogenesis of cancer cachexia are limited. GH resistance, with a progressive increase of GH and a steady decrease of IGF-I levels, was initially described in patients with lung cancer, which correlated to the advancing stage of cancer (Mazzoccoli *et al.* 1999). A subsequent study reported the presence of GH resistance with respect to hepatic IGF-I production in lung cancer patients most of whom had lost weight and lean mass without marked reduction in food intake; in addition, there was an intermittent increase in IGFBP-3 proteolysis, which might be regulated by IL-6 (Crown *et al.* 2002).

In the present issue of the *British Journal of Nutrition*, the paper presented by Huang *et al.* (2005) contributes further to the work in this field. The authors have studied the GH–IGF-I axis disturbance, particularly GH resistance, in gastrointestinal cancer patients with or without cachexia. The pattern of acquired GH resistance was observed only in colorectal cancer patients with cachexia, but not in non-cachectic cancer patients, and it could be reversed after surgical removal of the tumour, reflected by increased IGF-I levels with no major changes in body weight and GH levels. These findings indicate that GH resistance developed in cachectic colorectal cancer patients is likely to be caused by the tumour rather than an adaptation to malnutrition. However, in cachectic patients with gastric cancer, apparent GH resistance has not been found; moreover, the major increases in GH levels before and after the removal of the tumour appear to be stimulated by malnutrition characterized by markedly decreased BMI.

Taken together, the studies by Haung *et al.* (2005) and others suggest that abnormalities of the GH–IGF-I axis are involved in cancer cachexia. More importantly, these changes are not unified but might be influenced by different factors including the tumour type, nutritional status and inflammatory cytokines. A better understanding of the regulation and pathophysiological significance of acquired GH resistance should help to direct therapeutic interventions to restore anabolic/catabolic balance in cancer cachexia.

Chen Bing

Neuroendocrine & Obesity Biology Unit
School of Clinical Sciences
University of Liverpool
Liverpool L69 3GA, UK

bing@liverpool.ac.uk

References

Anker SD, Volterrani M, Pflaum CD, *et al.* (2001) Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. *J Am Coll Cardiol* **38**, 443–452.

Argiles JM, Busquets S & Lopez-Soriano FJ (2003) Cytokines in the pathogenesis of cancer cachexia. *Curr Opin Clin Nutr Metab Care* **6**, 401–406.

Bereket A, Lang CH, Blethen SL, Gelato MC, Fan J, Frost RA & Wilson TA (1995) Effect of insulin on the insulin-like growth factor system in children with new-onset insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* **80**, 1312–1317.

Bing C, Taylor S, Tisdale MJ & Williams G (2001) Cachexia in MAC16 adenocarcinoma: suppression of hunger despite normal regulation of leptin, insulin and hypothalamic neuropeptide Y. *J Neurochem* **79**, 1004–1012.

Boulware SD, Tamborlane WV, Matthews LS & Sherwin RS (1992) Diverse effects of insulin-like growth factor I on glucose, lipid, and amino acid metabolism. *Am J Physiol* **262**, E130–E133.

Cicoira M, Kalra PR & Anker SD (2003) Growth hormone resistance in chronic heart failure and its therapeutic implications. *J Card Fail* **9**, 219–226.

Cioffi WG, Gore DC, Rue LW 3rd, Carrougher G, Guler HP, McManus WF & Pruitt BA Jr (1994) Insulin-like growth factor-1 lowers protein oxidation in patients with thermal injury. *Ann Surg* **220**, 310–316; discussion 316–319.

Clemmons DR, Klibanski A, Underwood LE, McArthur JW, Ridgway EC, Beitins IZ & Van Wyk JJ (1981) Reduction of plasma immunoreactive somatomedin C during fasting in humans. *J Clin Endocrinol Metab* **53**, 1247–1250.

Cohen P, Clemmons DR & Rosenfeld RG (2000) Does the GH–IGF axis play a role in cancer pathogenesis? *Growth Horm IGF Res* **10**, 297–305.

Crown AL, Cottle K, Lightman SL, Falk S, Mohamed-Ali V, Armstrong L, Millar AB & Holly JM (2002) What is the role of the insulin-like growth factor system in the pathophysiology of cancer cachexia, and how is it regulated? *Clin Endocrinol (Oxf)* **56**, 723–733.

Cwyfan Hughes SC, Cotterill AM, Molloy AR, Cassell TB, Braude N, Hinds CJ, Wass JA & Holly JM (1992) The induction of specific proteases for insulin-like growth factor-binding proteins following major heart surgery. *J Endocrinol* **135**, 135–145.

Dean HJ, Kellett JG, Bala RM, Guyda HJ, Bhaumick B, Posner BI & Friesen HG (1982) The effect of growth hormone treatment on somatomedin levels in growth hormone-deficient children. *J Clin Endocrinol Metab* **55**, 1167–1173.

Dewys WD, Begg C, Lavin PT, *et al.* (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* **69**, 491–497.

Ding H, Kopple JD, Cohen A & Hirschberg R (1993) Recombinant human insulin-like growth factor-I accelerates recovery and reduces catabolism in rats with ischemic acute renal failure. *J Clin Invest* **91**, 2281–2287.

Donaghy A, Ross R, Wicks C, Hughes SC, Holly J, Gimson A & Williams R (1997) Growth hormone therapy in patients with cirrhosis: a pilot study of efficacy and safety. *Gastroenterology* **113**, 1617–1622.

Durai R, Yang W, Gupta S, Seifalian AM & Winslet MC (2005) The role of the insulin-like growth factor system in colorectal cancer: review of current knowledge. *Int J Colorectal Dis* **20**, 203–220.

Fearon KC & Moses AG (2002) Cancer cachexia. *Int J Cardiol* **85**, 73–81.

Fryburg DA, Jahn LA, Hill SA, Oliveras DM & Barrett EJ (1995) Insulin and insulin-like growth factor-I enhance human skeletal muscle protein anabolism during hyperaminoacidemia by different mechanisms. *J Clin Invest* **96**, 1722–1729.

Huang Q, Nai Y-J, Jiang Z-W & Li J-S (2005) Change of the growth hormone–insulin-like growth factor-I axis in patients with gastrointestinal cancer: related to tumour type and nutritional status. *Br J Nutr* **93**, 853–858.

Hussain MA, Schmitz O, Mengel A, Glatz Y, Christiansen JS, Zapf J & Froesch ER (1994) Comparison of the effects of growth hormone and insulin-like growth factor I on substrate oxidation and on insulin sensitivity in growth hormone-deficient humans. *J Clin Invest* **94**, 1126–1133.

Iida K, del Rincon JP, Kim DS, Itoh E, Coschigano KT, Kopchick JJ & Thorner MO (2004) Regulation of full-length and truncated growth hormone (GH) receptor by GH in tissues of lit/lit or bovine GH transgenic mice. *Am J Physiol Endocrinol Metab* **287**, E566–E573.

Jenkins RC & Ross RJ (1998) Acquired growth hormone resistance in adults. *Baillieres Clin Endocrinol Metab* **12**, 315–329.

Jones JI & Clemmons DR (1995) Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* **16**, 3–34.

Kaaks R & Lukanova A (2001) Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc* **60**, 91–106.

Mazzoccoli G, Giuliani A, Bianco G, De Cata A, Balzanelli M, Carella AM, La Viola M & Tarquini R (1999) Decreased serum levels of insulin-like growth factor (IGF)-I in patients with lung cancer: temporal relationship with growth hormone (GH) levels. *Anticancer Res* **19**, 1397–1399.

Oster MH, Fielder PJ, Levin N & Cronin MJ (1995) Adaptation of the growth hormone and insulin-like growth factor-I axis to chronic and severe calorie or protein malnutrition. *J Clin Invest* **95**, 2258–2265.

O'Sullivan U, Gluckman PD, Breier BH, Woodall S, Siddiqui RA & McCutcheon SN (1989) Insulin-like growth factor-1 (IGF-1) in mice reduces weight loss during starvation. *Endocrinology* **125**, 2793–2794.

Rinderknecht E & Humbel RE (1978) Primary structure of human insulin-like growth factor II. *FEBS Lett* **89**, 283–286.

Schaur RJ, Fellier H, Gleispach H, Fink E & Kronberger L (1979) Tumor host relations. I. Increased plasma cortisol in tumor-bearing humans compared with patients with benign surgical diseases. *J Cancer Res Clin Oncol* **93**, 281–285.

Skjaerbaek C, Frystyk J, Orskov H, Kissmeyer-Nielsen P, Jensen MB, Laurberg S, Moller N & Flyvbjerg A (1998) Differential changes in free and total insulin-like growth factor I after major, elective abdominal surgery: the possible role of insulin-like growth factor-binding protein-3 proteolysis. *J Clin Endocrinol Metab* **83**, 2445–2449.

Tisdale MJ (2002) Cachexia in cancer patients. *Nat Rev Cancer* **2**, 862–871.

Todorov P, Cariuk P, McDevitt T, Coles B, Fearon K & Tisdale M (1996) Characterization of a cancer cachectic factor. *Nature* **379**, 739–742.

Tomas FM, Knowles SE, Owens PC, Read LC, Chandler CS, Gargosky SE & Ballard FJ (1991) Increased weight gain, nitrogen retention and muscle protein synthesis following treatment of diabetic rats with insulin-like growth factor (IGF)-I and des(1-3)IGF-I. *Biochem J* **276**, 547–554.