IGF2 and cancer

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Abstract

Insulin-like growth factor 2 (IGF2) is a 7.5 kDa mitogenic peptide hormone expressed by liver and many other tissues. It is three times more abundant in serum than IGF1, but our understanding of its physiological and pathological roles has lagged behind that of IGF1. Expression of the IGF2 gene is strictly regulated. Over-expression occurs in many cancers and is associated with a poor prognosis. Elevated serum IGF2 is also associated with increased risk of developing various cancers including colorectal, breast, prostate and lung. There is established clinical utility for IGF2 measurement in the diagnosis of non-islet cell tumour hypoglycaemia, a condition characterised by a molar IGF2:IGF1 ratio > 10. Recent advances in understanding of the pathophysiology of IGF2 in cancer have suggested much novel clinical utility for its measurement. Measurement of IGF2 in blood and genetic and epigenetic tests of the IGF2 gene may help assess cancer risk and prognosis. Further studies will determine whether these tests enter clinical practice. New therapeutic approaches are being developed to target IGF2 action. This review provides a clinical perspective on IGF2 and an update on recent research findings.

Key Words

- IGF2
- cancer
- non-islet cell tumour hypoglycaemia

Introduction

Research during the 1960s discovered an insulin-like factor that could not be abolished by anti-insulin antibodies (Froesch et al. 1963). This was called non-suppressible insulin-like activity (NSILA). NSILA had the same properties as sulphation factor, discovered in 1957, required for incorporation of sulphate into cartilage (Salmon & Daughaday 1957). It was renamed somatomedin (Daughaday et al. 1972), and when sequenced, it was found to consist two peptides (Rinderknecht & Humbel 1976). These were named insulin-like growth factor (IGF) 1 and 2 because of their homology with insulin and similar metabolic actions. Our understanding of the pathophysiology of IGF2 lags behind that of IGF1, but there have been significant advances in recent years. The purpose of this review is to provide the reader with a perspective and update on IGF2, with respect to its role in cancer and clinical utility for its measurement.

The IGFs are part of a complex system, the components of which act together to influence growth. The system consists of insulin, both IGFs, their cell surface receptors and IGF binding proteins (IGFBPs). The IGFBPs are a family of six proteins that bind IGFs in serum (Clemmons 1998). They transport and sequester IGFs, regulating availability to receptors. About 75% of circulating IGFs exist as 150 kDa ternary complexes consisting of IGF1 or IGF2, IGFBP3 and acid-labile subunit (ALS), an 85 kDa protein synthesised in liver (Baxter 2001, Firth & Baxter 2002). These complexes are confined to the circulation because they are unable to cross capillary endothelia. Some IGFs exist as binary complexes (40–50 kDa) with IGFBPs that can leave the circulation, possibly functioning as a pericellular store of IGFs (Juul 2003). The remaining ‘free’ IGF (<1%) is considered bioactive. Given the complexity of the system, the
function of any individual component, such as IGF2, must be considered in the context of the whole system.

**IGF2**

Mature IGF2 is a 67 amino acid (7.5 kDa) peptide produced mainly by liver, but it is also secreted by most tissues where it can act in an autocrine or paracrine manner. There is considerable evidence that IGF2 regulates cell growth, it can act in an autocrine or paracrine manner. There is mainly by liver, but it is also secreted by most tissues where it can act in an autocrine or paracrine manner. Mature IGF2 is a 67 amino acid (7.5 kDa) peptide produced mainly by liver, but it is also secreted by most tissues.

Post-translational processing begins with cleavage of the signal peptide to yield pro-IGF2 (1–156). This is followed by O-linked glycosylation of the 89-residue E-domain that may promote further processing (Daughaday et al. 1993). Pro-IGF2 then undergoes sequential proteolysis to mature IGF2 (1–67) that lacks the E-domain. Prohormone convertase 4 (PC4) is the protease thought to cleave the E-domain. Incomplete processing of pro-IGF2 results in various peptides (10–18 kDa) containing all or part of the E-domain, known collectively ‘big’ IGF2. These are quantitatively IGF present in adults at a concentration of ~700 ng/ml (Humbel 1990), three times that of IGF1. Serum IGF2 is low in neonates, climbing in early childhood and then remaining at similar concentrations throughout life, although it may decrease slightly in healthy elderly subjects (Yu et al. 1999, Raynaud-Simon 2003). Concentrations are similar in both genders. Free IGF2 circulates at picomolar concentrations, similar to insulin. The portion of IGF2 bound to IGFBPs has a relatively long half-life (10–16 h) compared with that of free IGF2 (a few minutes) (Rajaram et al. 1997).

**IGF2 signalling**

IGF2 signals via three receptor complexes namely the IGF1 receptor (IGF1R), insulin receptor isoform A (IR-A) and the IGF1R-IR-A hybrid receptor (Fig. 2). IGF1R binds both IGFs with comparable and high affinity (Pandini et al. 2002). It is thought to mediate most of the biological effects of IGF2. IR-A is an alternatively spliced IR isoform that lacks exon 11 (11-1 encoding 12 amino acid residues at the C-terminus of the ligand-binding a subunit). This enables it to bind IGF2 with an affinity 15% of that for insulin, much higher than its affinity for IGF1 (Frasca et al. 1999, Nakae et al. 2001). While insulin binding stimulates glucose uptake, IGF2 binding is mitogenic (Belfiore et al. 2009). Although IR-A is widely expressed throughout life, its physiological role in adults is unclear.

In common with insulin and IGF1, binding of IGF2 to the IGF1R activates a receptor tyrosine kinase (RTK) associated with the β-subunit leading to an intracellular response (Belfiore & Malaguarnera 2011, Braun et al. 2011, LeRoith et al. 2011). Autophosphorylation of the β-subunit by the RTK recruits insulin receptor substrates (IRS) 1–4. Phosphatidylinositol 3-kinase (PI3-K) then binds to IRS1 via its regulatory subunit and is activated, in turn activating Akt (protein kinase B). This has a number of intracellular effects, which ultimately promote cell survival and mitogenesis. First, it inhibits apoptosis by inactivating BAD (BCL-2 antagonist of cell death). It also phosphorylates tuberous sclerosis complex (TSC1/2) leading to activation of mammalian target of rapamycin.

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**Figure 1**

Structure and processing of prepro-IGF2. The IGF2 gene (30 kb) is located on 11p15.5 comprising nine exons. Exons 7, 8 and 9 are encoding. Translation generates prepro-IGF2 (180 AAs, 20.1 kDa) consisting of five domains (A, B, C, D and E) and a 24-residue N-terminal signal peptide. Proteolysis of the signal peptide by signal peptidase yields pro-IGF2 (1–156). The C-terminal E-domain is glycosylated promoting further processing. Sequential proteolysis removes the E-domain giving mature IGF2 (1–67) that is secreted. Incompletely processed pro-IGF2 peptides (10–18 kDa) containing all or part of the E-domain are also secreted making up 10–20% of total circulating IGF2. These peptides are called ‘big’ IGF2.
(mTOR) and subsequent ribosomal protein synthesis that is required for mitogenesis. Akt also has the metabolic action of leading to GLUT4 translocation, which promotes cellular glucose uptake.

By recruiting other adaptor proteins to the receptor complex, ligand activation of IGF1R also leads to activation of the MAPK pathway that transmits the proliferative signals generated at the cell surface to the nucleus. It causes the change in expression of proteins required for cellular proliferation. Phosphorylation of IRS proteins recruits the adaptors Shc and growth factor receptor-bound protein 2 (Grb2), which along with son-of-sevenless form a complex activating the GTP binding protein Ras. There is further phosphorylation and activation of Raf-1 and the kinases (MEK1/2 and ERK1/2) that leads to the activation of transcription factors involved in cell proliferation.

The tumour suppressor phosphatase and tensin analogue (PTEN) dephosphorylates and inhibits PI3-K. It also inhibits Shc and mTOR. It, therefore, inhibits the downstream mitogenic pathways activated by PI3-K, thereby opposing the action of a number of growth factors including IGF2 (Gallagher & LeRoith 2010). In turn, IGF2 signalling appears to increase PTEN expression, which may be a form of feedback loop (Moorehead et al. 2003). These pathways are described in detail elsewhere (Belfiore & Malaguarnera 2011).

**Physiological regulation of IGF2**

Before discussing dysregulation of IGF2 in cancer, it is necessary to cover its physiological regulation. Regulation of both IGF2 expression and IGF2 action are complex and multifactorial. This complexity appears to permit fine-tuning of responses and to prevent excessive IGF2 action that could lead to disease.

Genetic factors play a significant role in the regulation of IGF2. The proportion of its variance attributable to genetic factors is 66%, compared with 38% for IGF1 (Harrela et al. 1996). Transcription is regulated by genomic imprinting, an epigenetic mechanism that restricts expression to the paternal allele in most tissues. Imprinting is achieved by methylation of the differentially methylated region (DMR) on the maternal allele.
It prevents excessive expression of IGF2, which could lead to proliferation and tumours. IGF2 is transcribed from four promoters (P1–P4) in a tissue-specific manner. During embryogenesis, transcription occurs from P2–P4 resulting in monoallelic expression. In adults, there is also expression from P1 in liver which is biallelic (Vu & Hoffman 1994) accounting for the high circulating IGF2 concentrations in adults. An antisense IGF2 transcript (IGF2AS) has been described, which is also maternally imprinted (Vu et al. 2003). It is expressed at levels similar to IGF2 but its regulatory role is unknown.

By sequestering both IGFs in the circulation, IGFBP3 inhibits their mitotic effects (Nickerson et al. 1997) and insulin-like actions (Boisclair et al. 2001). IGFBP2 accounts for most of the remaining IGF2 binding in the circulation (Clemmons et al. 1991). IGFBP1 and IGFBP2 are thought to regulate free IGF2 (Clemmons 1997). IGFBPs are themselves subject to regulation by various hormones, including insulin and IGFs (Kelley et al. 1996). GH stimulates hepatic IGFBP3 and ALS synthesis that, by increasing ternary complex formation, in turn increases total IGF2 concentrations (Woll et al. 1994). IGF2 is, therefore, in part GH dependent but is less GH dependent than IGF1, which explains the absence of a pubertal increase in its serum concentrations (Zapf et al. 1981). IGFBPs have independent effects on cell adhesion and migration (Kelley et al. 1996) and effects enhancing the action of IGFs (Clemmons 1997). Mechanisms release IGFs from the complexes enabling receptor interaction (Firth & Baxter 2002). These include IGFBP proteolysis (Muller et al. 1994), phosphorylation and binding to the extracellular matrix (LeRoith & Butler 1999). IGFBPs may have biological actions of their own (Jones & Clemmons 1995, Firth & Baxter 2002, Martin & Baxter 2011).

Cellular responsiveness to IGF2 is influenced by changes in receptor expression. Increased IR-A expression during embryogenesis (Belfiore et al. 2009) and increased IR-A:IR-B ratio during de-differentiation (Entingh et al. 2003) promote its action. IGF2 also binds to the widely expressed IGF2R, a 250 kDa monomeric, cell surface protein. It is thought to promote endocytosis and lysosomal degradation of IGF2, thereby antagonising its action and acting as a tumour suppressor (Brown et al. 2009). IGF2R also binds lysosomal enzymes intracellularly, transporting them from the Golgi to lysosomes (Kornfeld 1992). The IGF2R gene, like IGF2, is imprinted but expressed from the maternal allele. This reciprocal imprinting may regulate the relative abundance of the two proteins. A soluble form of IGF2R cleaved from the cell surface binds IGF2 in serum and is thought to reduce IGF2 bioactivity in vivo (Ellis et al. 1996, Scott & Weiss 2000).

Because the IGFs promote growth, it is logical that they are both nutritionally regulated, their concentrations indicating the availability or otherwise of substrate from the diet. Down-regulation of IGF2 during starvation may protect the individual from hypoglycaemia, which would occur if its concentration did not decrease in parallel with ternary complexes. Specific nutrients also influence IGF2, notably down-regulation by vitamin C (Lee et al. 2008) and vitamin D (Huynh et al. 1998).

Cancer development

Sustained IGF action promotes carcinogenesis (Renehan et al. 2006). IGF1 and IGF1R are the components of the system best studied in this process (Larsson et al. 2005), but growing evidence from in vitro and in vivo studies has shown that IGF2 also promotes cancer development and progression (Yu & Rohan 2000).

Over-expression of IGF2

As cells age, dysregulation of the DMR on the maternal chromosome causes loss of imprinting (LOI) of IGF2 with over-expression and increased sensitivity to IGF2 signalling (Fu et al. 2004, Kaneda et al. 2007). This exposes cells to excessive IGF2 and the more potent pro-IGF2 (Kalla Singh et al. 2008) that promote growth and anti-apoptosis in an autocrine manner (Gallagher & LeRoith 2010). Studies in animals have demonstrated that sustained IGF2 action increases the risk of transformation. Transgenic animals over-expressing IGF2 were at increased risk of developing mammary gland adenocarcinoma (Bates et al. 1995) and lung cancer (Moorehead et al. 2003b). IGF2 caused earlier and more aggressive cancers (Rogler et al. 1994, Pravtcheva & Wise 1998). Conversely, animals with low IGF2 concentrations lived longer, with a lower incidence of tumours (Bartke et al. 2002). Other mechanisms of IGF2 over-expression have been described. For example, the morphogen sonic hedgehog (Shh) is inappropriately activated in some tumours, increasing expression of IGF2 and other genes involved in regulation of cell growth (Ingram et al. 2002, Ruiz et al. 2002). IGF2 expression is also promoted by defective expression of the transcriptional repressor WT1 (Ward 1997). It should be noted that LOI of IGF2 is not exclusive to cancer cells but is also commonly observed in normal neonates (Rancourt et al. 2013) and adult humans (Belharzem et al. 2012).
In humans, there is extensive evidence for IGF2 dysregulation in tumours. LOI is a common epigenetic abnormality in breast (Hartmann et al. 2005), oesophageal (Zhao et al. 2009) and ovarian cancer (Murphy et al. 2006) and acute myeloid leukaemia (Wu et al. 1997). In Wilms’ tumours, there is increased IGF2 expression in 50% of cases, usually due to LOI (Reeve 1996). Increased IGF2 expression is particularly common in mesenchymal tumours (Steigen et al. 2009). The frequency of increased expression was greatest in Ewing’s sarcoma and tenosynovial giant cell tumours whereas levels of expression, as assessed by immunoreactivity, were greatest in solitary fibrous tumours. IGF2 was one of 31 genes up-regulated in hepatitis B virus-associated hepatocellular carcinoma (HCC; Couvert et al. 2008), suggesting a role in hepatocarcinogenesis. More recently, work on peripheral blood mononuclear cells found that IGF2 methylation decreased during progression from cirrhosis to HCC (Couvert et al. 2012). LOI of IGF2 is a common finding in colon cancer (Cui et al. 2003, Cui 2007). It is significantly associated with family history of the disease and appears to be a heritable risk factor rather than being acquired because of environmental exposure (Cruz-Correa et al. 2004).

Study of the Beckwith–Wiedemann syndrome (BWS), in which LOI of IGF2 was first described, has provided further evidence for a link between IGF2 dysregulation and cancer development. This is a rare congenital syndrome characterised by placental and postnatal overgrowth. There may be gigantism, macroglossia, organomegaly and a predisposition to tumours, in particular Wilms’ tumour (Shapiro et al. 1982). Most patients have gene deletions resulting in IGF2 LOI. This causes biallelic expression with increased IGF2 concentrations (Sparago et al. 2004). In 20% of patients, IGF2 over-expression results from uniparental disomy in which two paternal IGF2 gene copies are inherited (Biliya & Bulla 2010). Excessive IGF2 is thought to be responsible for the clinical features of BWS because similar features were observed in a mouse transgenic model over-expressing IGF2 (Sun et al. 1997).

In some tumours, over-expression of IGF2 is insufficient for tumorigenesis (Hahn et al. 2000). Additional defects may be required such as loss of repressor function, changes in promoters (Yu & Rohan 2000) or receptor dysregulation (Algire et al. 2011). IGF2R defects are also implicated in cancer development. Imprinting makes IGF2R susceptible to mutations because a lethal mutation affecting the single active gene copy results in an absence of functional protein. IGF2R mutations causing loss of function of the protein have been described in numerous cancers (De Souza et al. 1997). They often occur early in carcinogenesis, predisposing to cancer presumably via loss of restraint on IGF2 (Biliya & Bulla 2010). Polymorphisms of IGF2R are also linked to increased risk of oral cancer (Yoon et al. 2012), colonic cancer (Probst et al. 2009) and HCC (Morcavallo et al. 2012) possibly because of impaired IGF2 clearance.

Epidemiological studies have linked elevated IGF1 and decreased IGFBP3 to common epithelial cancers (Maki 2010), but few such studies have measured IGF2. In one large follow-up study on breast cancer in postmenopausal women, serum IGF2 and IGFBP3 but not IGF1 were positively associated with oestrogen receptor-positive breast cancer risk (Gronbaek et al. 2004), although there was no overall association between IGF2 and breast cancer risk. In the prostate cancer prevention study, neither IGF1 nor IGF2 was associated with prostate cancer (Neuhouser et al. 2013) but elevated serum IGFBP2 was a risk factor for low-grade disease. A small study on early-stage breast cancer reported elevated free IGF1 and IGF2 but total IGF2 was reduced (Espelund et al. 2008). IGF2 demands further assessment in epidemiological studies of cancer.

**IGF2 signalling in cancer development**

The signalling mechanisms whereby IGF2, IGF1 and insulin may promote cancer development have been extensively studied. Pathways are now known whereby IGF2-mediated activation of IGF1R or hybrid receptors may promote tumorigenesis (Alvino et al. 2011, Pierre-Eugene et al. 2012). The MAPK pathway appears to be the main pathway whereby IGF2 and other ligands of the IGF1R activate genes concerned with cell proliferation causing mitogenesis. The PI3-K/Akt pathway is also activated, leading to reduced apoptosis and increased cell survival. It appears to play a supportive role in the process. Sustained IGF2-mediated autocrine IGF1R signalling has also been suggested as the mechanism of sarcoma development in BWS (Ratajczak 2012).

IR-A activation has mitogenic effects and is another mechanism whereby IGF2 may promote tumorigenesis. IGF2 action through IR-A appears to differentially influence gene expression compared with insulin acting through the same receptor (Pandini et al. 2004). In addition, quantitative proteomic studies have shown that IGF2 binding to IR-A recruits a different but overlapping set of substrates from insulin (Morcavallo et al. 2011). It has been suggested that the differences in IR-A phosphorylation following IGF2 binding compared with insulin may protect IRS proteins from down-regulation, enabling the signal to be sustained (Belfiore & Malaguarnera 2011). Such prolonged
signalling could be damaging. The elevated insulin concentrations observed in patients with type 2 diabetes could therefore act through IR-A to promote cancer development, accounting for the excess of cancers observed in this condition. However, this mechanism is unproven. IGF2 action appears to be favoured by the increased IR-A:IR-B ratio that occurs with ageing (Serrana et al. 2005) and may increase the risk of tumorigenesis. Increased IGF2 action through IR-A is also linked to reduced vertebrate lifespan (Belfiore et al. 2009).

Recent work on the transcription factor E2F3 has suggested that it has a role in causing increased IGF2 expression in human cancers (Lui & Baron 2013). In mice, E2F3 is thought to be responsible for the decline in IGF2 expression, which occurs postnatally. E2F3 expression declined postnatally whereas restoration of its expression restored IGF2 expression. Microarray analysis in humans observed E2F3 and IGF2 expression to decline with age but bladder and prostate cancers that over-expressed the transcription factor also over-expressed IGF2 (Lui & Baron 2013). This work suggests that E2f3 is a contributing factor in age-related decline in IGF2 expression and is also a factor driving its pathological over-expression in cancers.

Tumour suppressors

The tumour suppressor PTEN is commonly mutated in human cancers. Absence of its action permits increased mitogenic signalling in the pathways downstream of PI3-K. The sustained mitogenic action will tend to promote carcinogenesis. In studies of breast cancer cells, loss of PTEN action appears to increase IGF2 signalling through IGF1R and IR-A (Perks et al. 2007). There is increasing evidence for interaction between IGF2 and p53 in cancer development. Normally, IGF2 transcription is repressed by the tumour suppressor p53 (Zhang et al. 1996, 1998), which also increases IGFBP3 (Buckbinder et al. 1995) and suppresses IGF1R expression (Werner et al. 1996). Decreased activity of p53 in tumours, therefore, increases both IGF2 expression and action. Recent data suggest that increased IGF2 signalling favours tumour development by suppressing activity of the p53 pathway (Clermont et al. 2012). Because the p53 pathway is inactive in most cancers, these findings suggest potential therapeutic benefit in a wide range of cancers from targeting IGF2 signalling.

Obesity

It is well recognised that obesity and diabetes predispose to cancer and the IGF system is believed to have a causal role in the link (Renehan et al. 2006, Byers & Sedjo 2011). Although the role of IGF2 is unclear, studies have observed elevated concentrations in obese subjects, presumably an appropriate response to excessive energy provision (Frystyk et al. 1999, Espelund et al. 2005, Fowke et al. 2010). IGF2 concentrations correlated with BMI. Free IGF2 concentrations paralleled these changes, suggesting that total IGF2 can be considered a surrogate for bioactive IGF2 in obesity (Frystyk et al. 1999). Subjects with type 2 diabetes, as well as obesity, had even higher IGF2 concentrations (Jeyaratnaganthan et al. 2010). Clearly, the increased IGF2 bioactivity could be detrimental by causing sustained mitogenic signalling. Weight reduction resulted in decreases in serum total IGF2 and pro-IGF2, independent of the type of diet (Belobrajdic et al. 2010). These decreases may reflect first reduced synthesis in response to reduced dietary energy provision and secondly the increased insulin sensitivity, which occurs upon weight reduction. A recent meta-analysis of epidemiological studies reported that intentional weight loss could reduce cancer incidence (Byers & Sedjo 2011). Use of the insulin sensitizer metformin has also been linked to reduced incidence of cancer (Libby et al. 2009) and better treatment response in breast cancer (Gallagher & LeRoith 2010). While the mechanisms are unknown, these findings have important therapeutic implications. The role of IGF2, if any, in the increased cancer incidence of obesity needs to be clarified by future studies.

Parental obesity may influence fetal health and ultimately cancer risk, through epigenetic changes in IGF2. Reduced IGF2 DMR methylation in umbilical cord blood was associated with increased IGF2 concentrations (Hoyo et al. 2012a). This association was stronger in infants of obese mothers. Increased IGF2 concentrations were significantly associated with high birth weight. In another study, placental IGF2 methylation was associated with fetal weight (St-Pierre et al. 2012). The IGF2 genotype and epigenotype was estimated to account for 31% of the variation in neonatal weight. These transgenerational effects are not confined to maternal nutritional status. Recently, paternal obesity was associated with hypomethylation of the IGF2 DMR in offspring (Soubry et al. 2013). Periconceptual parental weight therefore appears to influence epigenetic regulation of IGF2, which in turn regulates fetal IGF2 concentrations and weight. This may enable parental obesity to predispose to cancer later in the life of the infant. In animals, periconceptual dietary restriction of obese mothers can influence the epigenetic state of the IGF2 gene (Zhang et al. 2011). It is not known whether a similar effect occurs in humans. Exposure to
Environmental compounds during pregnancy can also potentially damage fetal health by causing epigenetic changes. Recent studies have observed that maternal exposure to bisphenol A (Susiarjo et al. 2013) and antibiotics (Vidal et al. 2013) altered IGF2 DMR methylation. The former was associated with abnormal placental development and the latter with lower infant birth weight.

**Cancer progression**

There is extensive evidence that increased IGF2 expression by tumours is associated with a poorer prognosis, for example greater mortality in breast cancer (Kalla Singh et al. 2010a), shorter time to disease recurrence in oesophageal cancer (Zhao et al. 2009) and more rapid disease progression in chronic myeloid leukaemia (Randhawa et al. 1998). Significant progress has been made in understanding the molecular mechanisms whereby IGF2 promotes tumour growth, leading to a poorer prognosis.

**Neovascularization**

IGF2 promotes neovascularization of tumours, without which growth would be inhibited by hypoxia (De Leon et al. 1992). Its expression appears to be hypoxia driven as part of a progression of angiogenic growth factors. Hypoxia-inducible factors up-regulate IGF2 which in turn up-regulates vascular endothelial growth factor (VEGF) leading to angiogenesis (Kim et al. 1998, Bae et al. 1999). IGF2 also promotes angiogenesis by stimulating differentiation of embryonic stem cells into endothelial cells (Piecewicz et al. 2012). Even when not expressed by the tumour itself, IGF2 may be detected in surrounding tissues, suggesting that it can act in a paracrine manner to promote growth (El-Badry et al. 1991). Increased IGF2 has also been observed in the transition zone between normal epithelium and preinvasive lesions originating from stromal cells and leucocytes (Heffelfinger et al. 1999). Recently, blockage of IGF2 expression caused down-regulation of VEGF and inhibited growth (Yao et al. 2012). These findings make IGF2 a key therapeutic target.

**Receptors and signalling**

IGF2 promotes cancer cell growth in part via the IGF1R. Signalling through this receptor has been reviewed in detail elsewhere (Kim et al. 2009, Djogue et al. 2013) and is mentioned only briefly here. IGF1R has an established role in tumour progression, its copy number negatively associated with survival time (Natarajan et al. 2006). Its increased expression by cancer cells is associated with over-expression of IGF2 and tendency to metastasize (Guerra et al. 1996). Mutations causing constitutive activation of IGFIR are rare. This emphasises the importance of its activation by ligands, including IGF2, in cancer progression (Kim et al. 2009).

IR-A is the predominant isoform expressed in cancer cells, its expression highest in de-differentiated malignancies. A high IR-A:IR-B ratio favours IGF2 action, impairing differentiation (Vella et al. 2002, Entingh et al. 2003, Belfiore et al. 2009) and is associated with disease progression (Frasca et al. 1999, Belfiore et al. 2009). The cause of this aberrant expression is unknown but insulin resistance up-regulates IR-A in cancer cells (Algire et al. 2011). Increased IGF2/IR-A signalling can occur following therapeutic blockage of IGF1R causing resistance to treatment (Garofalo et al. 2011). In cancer cells, IGF2 can exert all its effects through IR-A. For example, in the leiomyosarcoma cell line SKUT-1, which expresses no IGF1R, IGF2 signals exclusively through IR-A (Sciacca et al. 2002). IGF2 appears to be more damaging than insulin when signalling through IR-A (Morcavallo et al. 2012). Unlike insulin, sustained IGF2 exposure failed to cause down-regulation of the intracellular signalling protein IRS1. Moreover, IGF2 was less effective than insulin at promoting internalisation of IR-A. These differences may enable its mitogenic stimulus to be sustained. It has, therefore, been hypothesised that IGF2 acts in an autocrine loop with IR-A expression enhancing cancer cell growth (Fig. 3). This has been observed in trophoblastic malignancies (Altieri et al. 2003), and thyroid cancer (Vella et al. 2002) and may contribute to chemoresistance (Gualberto & Pollak 2009).

**Figure 3**

Autocrine loop of IGF2 action in cancer progression. IGF2 can be produced in excess by tumour cells because of loss of imprinting (LOI) of the IGF2 gene. IGF2 produced by tumour cells can act in an autocrine manner by binding to isoform A of the insulin receptor (IR-A). This results in stimulation of mitosis and continued production of IGF2. Sustained intracellular signalling and impaired IR-A internalisation potentially enable a vicious cycle of increasing growth and IGF2 production.
Loss of IGF2R is associated with a poor prognosis (Jamieson et al. 2003, Pavelic et al. 2003). The aggressive phenotype may be caused both by excessive IGF2 and over secretion of lysozomal proteases that promote tumour invasion (Probst et al. 2009). Conversely, increased IGF2R expression is associated with a better outcome from disease, possibly because of enhanced clearance of IGF2 (Kalla Singh et al. 2010b). Recent evidence suggests that IGF1R/IR-A hybrid receptors have proliferative effects in cancer cells (Cheng et al. 2009). IGF2 may, therefore, also promote tumour growth by signalling through these receptors.

**IGF binding proteins**

IGFBPs secreted by cancer cells may either enhance or inhibit growth by modulating IGF2 action. Over-expression of IGFBP2 and IGFBP5 has been associated with increased IGF action and poorer cancer prognosis (Pollak 2008). For example, increased IGFBP2 secretion by leukaemic T cells in response to IGF2 promoted growth (Elmlinger et al. 1998). Increased proteolysis of IGFBP3 by breast cancer cells stimulated tumour growth by increasing local IGF availability. Protease activity was highest in patients with the most invasive tumours (Helle et al. 2001). Conversely, growth was inhibited by increased IGFBP3 expression in response to transforming growth factor β (TGFβ; Oh et al. 1995). This anti-proliferative effect was abolished by IGF2, which blocked TGFβ-induced binding of IGFBP3 to the cell surface. Increased IGFBP3 expression has also been reported as a mechanism whereby vitamin D opposes IGF2 action (Huynh et al. 1998).

**Steroidogenesis**

There is recent evidence that both IGF2 and insulin contribute to prostate cancer progression by increasing *de novo* steroidogenesis. IGF2 treatment of androgen receptor-expressing prostate cancer cell lines caused increased steroidogenesis leading to androgen receptor activation and prostate-specific antigen expression (Lubik et al. 2013). In the same study, increased IGF2 expression in prostate cancer tissue from patients was observed to accompany resistance to androgen deprivation therapy (ADT). In a previous study by the same group, insulin treatment of prostate cancer cell lines increased steroidogenic enzyme expression and testosterone secretion (Lubik et al. 2011). The authors hypothesised that increased steroidogenesis is a mechanism whereby elevated insulin concentrations that occur during ADT promote prostate cancer progression.

**Non-islet cell tumour hypoglycaemia**

Non-islet cell tumour hypoglycaemia (NICTH) is a rare paraneoplastic syndrome occurring in association with large or metastatic tumours, usually over 0.5 kg in size (Marks & Teale 1998). It has been reported in almost every type of tumour (de Groot et al. 2007). This diagnosis should always be considered when hypoglycaemia occurs in patients with advanced malignancy. The discussion here will be confined to IGF2-related hypoglycaemia, but it should be stated that NICTH can be caused by other factors, namely IR autoantibodies, cytokines and malignant invasion of the liver.

**Mechanism of hypoglycaemia**

Over-expression of IGF2 is the central event in NICTH. The serum concentrations of mature IGF2 and big IGF2 are increased in 30 and 70% of patients respectively (Hizuka et al. 1998). Big IGF2 contributes up to 60% of the total IGF2 present in NICTH. It retains 21 residues of the E-peptide (IGF2E (68–88)), which is non-glycosylated (Daughaday et al. 1993). The reason for impaired proteolytic processing of pro-IGF2 is unclear but recent studies have suggested mechanisms. First, processing may fail because of the absence of glycosylation (Daughaday et al. 1993). Secondly, the quantity of pro-IGF2 produced may overwhelm the proteolytic capacity of the tumour cells (Zapf 1993). In support of this, defective PC4 expression has been reported in a tumour causing NICTH (Tani et al. 2008). Increased serum concentrations of the E-domain have also been observed in patients with NICTH (Daughaday & Trivedi 1992b).

Various factors increase bioavailable IGF2 in NICTH. Big IGF2 binds to IGFBPs with the same affinity as does mature IGF2, but forms ternary complexes less readily, possibly because of reduced affinity for ALS (Daughaday 1996). Binary complexes with IGFBPs (40–50 kDa) are favoured, which can traverse the capillary endothelium (Bond et al. 2000). In addition, much big IGF2 remains unbound. Free IGF2 is increased up to 20-fold even when the total IGF2 concentration is normal (Frystyk et al. 1998). This is probably because of impaired ternary complex formation or displacement by big IGF2. Both bioavailable big IGF2 and mature IGF2 mimic the action of insulin (Daughaday et al. 1988). These increase glucose uptake into peripheral insulin target tissues and suppress hepatic glucose output, leading to hypoglycaemia. Free IGF2 also suppresses ketogenesis, which reduces the body’s ability to compensate for hypoglycaemia.
The serum β-hydroxybutyrate (BOHB) concentration therefore tends to be low.

Under normal circumstances, hypoglycaemia stimulates pituitary GH release in order to oppose insulin action. In NICTH, however, this effect is overridden by the suppressive effect of free IGF2 on the GH axis, causing low GH concentrations (LeRoith & Butler 1999). This may render the individual more susceptible to hypoglycaemia, although catecholamine secretion occurs normally (Eastman et al. 1992). Low GH also reduces hepatic synthesis of all ternary complex components, potentially resulting in a further increase in free IGF2. It has therefore been hypothesised that there is a vicious circle of increased production of big IGF2, impaired ternary complex formation and suppressed GH, leading to further reduction of ternary complex components (de Groot et al. 2007; Fig. 4).

Recent studies have provided new insights into the pathogenesis of NICTH. An in vitro study of IGF2 complex formation suggested that bioavailability of big IGF2 depends on the ratio with mature IGF2 (Qiu et al. 2010). Under physiological circumstances, with a big IGF2:mature IGF2 ratio of 0.24, big IGF2 preferentially formed complexes with IGFBP3 whereas mature IGF2 complexed with both IGFBP2 and IGFBP3. However, when the ratio was above 1, big IGF2 preferentially formed binary complexes with IGFBP2. The increased binary complex formation that occurs in the presence of excessive big IGF2 probably increases its bioavailability. Big IGF2 isoforms bind less readily to IGF2R, which may impair their clearance further increasing bioavailability (Greenall et al. 2013). Interestingly, NICTh and glucose intolerance were recently reported in the same patient (Thabit et al. 2011). The mechanism is unclear but prolonged IR stimulation by big IGF2 may cause post-receptor insulin resistance manifesting itself as impaired glucose tolerance. It remains unclear why IGF2-related hypoglycaemia is so rare given that IGF2 secretion by tumours is common.

Other clinical features A variety of other clinical features have been reported attributable to big IGF2 and mature IGF2. Acromegoid skin changes (Trivedi et al. 1995) and goitre (Thabit et al. 2011) are trophic effects possibly caused by prolonged IGFR1 activation. Hypoglycaemia may be caused by insulin-like action of IGF2 causing cellular uptake of potassium (Fukuda et al. 2006). Another characteristic feature of NICTh is elevation of IGFBP6, the mechanism of which is not understood but may be caused by the tumour itself (Elmlinger et al. 1998, Hoogwerf et al. 2013). Increased production of IGFBP6 has also been reported (Hoekman et al. 1999). Reported biochemical findings in NICTh are summarised in Table 1.

Treatment The treatment of choice in NICTh is surgery or debulking of the tumour to remove the underlying cause, namely IGF2 or big IGF2 production.
Medical treatments include chemotherapy, glucocorticoids (Baxter et al. 1995, Teale & Marks 1998), diazoxide (Mitchell et al. 1968), recombinant GH (Drake et al. 1998), glucagon (Phillips & Robertson 1993), somatostatin analogues (Perros et al. 1996) or combinations thereof. Of these, high-dose glucocorticoids are the most successful reducing both big IGF2 production and tumour size. Surgical removal of the tumour can return the IGF2:IGF1 ratio to normal, abolish the hypoglycaemia and restore normal GH and IGFBP3 concentrations (Zapf 1993, Perros et al. 1996). In addition, mature IGF2 climbs following treatment, suggesting that big IGF2 has a suppressive effect on its concentrations (Zapf et al. 1992).

**Clinical utility for IGF2 and related tests in cancer**

In order for IGF2 measurement to be worthwhile in any clinical context, it must guide the management of the patient. The high cost of IGF2 testing emphasises the importance of its utility being clear. For the purpose of discussion, the utility of IGF2 and related tests is divided into established and potential. These are summarised in Table 2.

### Established utility

The only established indications for IGF2 measurement are in diagnosis and monitoring of NICTH. Because of the rarity of NICTH, IGF2 measurement is infrequently requested, the analysis being confined to specialist centres or research laboratories. The biochemical findings in NICTH are hypoglycaemia in the presence of appropriately suppressed insulin and C-peptide concentrations but inappropriately low GH and IGF1. While serum IGF2 concentrations are normal in about 70% of cases, IGF1 is invariably low (Hizuka et al. 1998). This causes the IGF2:IGF1 ratio to be >10 (normal <3) which is the key diagnostic finding (Marks & Teale 1998). Besides NICTH, the only possible cause of an elevated IGF2:IGF1 ratio is hypoglycaemia associated with sepsis. This should be straightforward to distinguish from NICTH because sepsis reduces hepatic synthesis of IGFs causing both their concentrations to decrease.

The BOHB concentration is typically below 600 μmol/l (Marks & Teale 1998). Levels of non-esterified fatty acids (NEFA) are also low. In a hypoglycaemic adult, the finding of low BOHB in the presence of suppressed insulin and C-peptide levels suggests the presence of an agent mimicking insulin and indicates measurement of the IGF2:IGF1 ratio. Measurement of IGFBP2 is a useful part

### Potential utility

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GIST, gastrointestinal stromal tumour; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IGF2, insulin-like growth factor 2; IGF2R, type 2 IGF receptor gene; LOI, loss of imprinting; NICTH, non-islet cell tumour hypoglycaemia.
of the diagnostic process. Ideally big IGF2 and free IGF2 should be measured but assays for these are not widely available in clinical laboratories. In making the diagnosis, all biochemical findings should be interpreted in clinical context. The diagnosis can be further confirmed by the response of the biochemical parameters to treatment.

Potential utility
Recent research findings suggest novel uses for IGF2 measurement and related tests in patients with cancer. These are not yet established in clinical practice, but future studies will clarify their utility. It is likely that the need for such tests will increase in the near future once treatments targeting IGF2 are established. Tests may be needed firstly to determine which patients will benefit from treatment and secondly to monitor the response.

Early diagnosis and monitoring
The observation and secondly to monitor the response to determine which patients will benefit from treatment targeting IGF2 are established. Tests may be needed firstly to determine whether serum concentrations reflect their activity in the tumour. Over-expression of IGF2 as assessed by tumour IGF2 mRNA content has been strongly linked to reduced disease-free survival in adrenocortical tumours (Gicquel et al. 2001). Loss of IGF2R expression in some cancers (Ellis et al. 1996, Jamieson et al. 2003) suggests prognostic utility for measurement of IGF2R in the circulation or immunohistochemically. Detection of IGF2R mutations may also be of value in managing cancer (Pavelic et al. 2003). One IGF2 polymorphism was recently observed to independently predict tumour recurrence following surgery for HCC (Lee et al. 2012).

As the bioactive component, free IGF2 is potentially more relevant prognostically than total IGF2 (Frystyk et al. 1998). It is technically difficult to measure but has been measured using ultrafiltration by centrifugation to isolate the free fraction followed by time-resolved fluoroimmunooassay (Frystyk et al. 1994) and has also been measured using a neutral C-18 Sep-Pak extraction procedure (Daughaday et al. 1995). Rather than measuring free IGF2 directly, an alternative approach may be to measure IGF2 as a ratio with IGFBP1 or IGFBP2, which indirectly reflects bioactivity. The prognostic value of these ratios has not been studied but the IGF1:IGFBP1 ratio has been found to predict therapeutic benefit of an IGF1R MAB (Gualberto et al. 2011). Although free IGF2 has been measured in patients with cancer (Daughaday et al. 1995, Frystyk et al. 1998), measurement of total IGF2 currently appears to suffice for clinical utility. In time, utility will likely emerge for free IGF2 measurement, which will drive the development of new assays.
A new approach to assessment of prognosis may be to examine tumour cells isolated from peripheral blood. This technique was used in patients with prostate cancer to examine expression of multiple epithelial–mesenchymal transition genes including IGF2 (Chen et al. 2013). The expression of these genes was associated with metastatic, treatment-resistant cancer.

**Prediction of cancer risk**  Studies suggest that IGF2 measurement and genetic tests may have a role in prevention of cancer. Increased IGF2 concentrations in blood appear to predict development of colonic cancer in women (Hunt et al. 2002). More recently, a study investigated the ability of a number of IGF system components to predict colorectal cancer risk (Gao et al. 2012). IGF2 was the most effective predictor. IGF2 does not act in isolation during carcinogenesis but is modulated positively and negatively by other components of the system, which may themselves have prognostic value. For example, over-expression of IGF1R is associated with more aggressive tumours (Hakam et al. 1999) and IGFBP3 may have a role both in early diagnosis (Darago et al. 2011) and prediction of death (Rowlands et al. 2012) in prostate cancer and in prediction of risk of colorectal cancer (Wu et al. 2011). In view of this, a more accurate assessment of an individual’s cancer risk or prognosis may be to combine a panel of measurements as an index.

**IGF2 LOI is an early event in cancer development, the detection of which may enable assessment of cancer risk.** A pilot study reported that colorectal cancer risk could be predicted by IGF2 LOI in peripheral blood lymphocytes (Cui et al. 2003). This requires further investigation by prospective studies to determine outcome and lead time in making the diagnosis but it raises the exciting possibility of being able to assess cancer risk using a non-invasive test (Cui 2007). Individuals testing positive could be targeted for regular colonoscopy. More recently, genetic studies of IGF2 were carried out in lymphocytes from patients with a history of prostate cancer (Belharazem et al. 2012). The study observed that uncoupling of IGF2 concentrations from imprinting status, rather than LOI alone, had the potential to identify individuals at risk of developing prostate cancer. In the same study, the IGF2 820 G/A genotype predicted prostate cancer diagnosis at a younger age. In view of the links between IGF2R polymorphisms and cancer (Hoyo et al. 2012b, Yoon et al. 2012), IGF2R testing may have a predictive role and demands further investigation. Recent research findings suggest much potential clinical utility for IGF2 testing in the context of liver cancer. The possibility of predicting hepatocarcinogenesis by genetic testing is perhaps the most exciting (Couvert et al. 2012).

Genomic assays that provide molecular signatures for multiple genes, including IGF2, may also predict cancer risk (Hoshida 2011). The Collaborative Oncological Gene-environment study has already detected more than 80 gene variants associated with increased risk of breast, prostate and ovarian cancers. This is a rational approach to prediction because IGF2 is only one of many genes working together to determine risk. These techniques could potentially be combined with traditional screening approaches to increase efficacy in disease detection. It is increasingly recognised that methylation patterns can be used as biomarkers for disease or predisposition to disease (Biliya & Bulla 2010). The Human Epigenome Project is underway to identify methylation patterns throughout the genome (www.epigenome.org, 2013).

**Therapeutic approaches**

The evidence discussed above has stimulated interest in cancer treatments targeting IGF2 action. IGF2 is an attractive therapeutic target because its apparently minor physiological role in adults suggests that ablation of its action carries little potential for disrupting normal processes. There have been exciting recent developments in therapies targeting IGF2, a full account of which is beyond the scope of this review. Interested readers are directed elsewhere (Gualberto & Pollak 2009, Heidegger et al. 2011).

Possible therapeutic targets are IGF2 itself, IGFBPs, receptors or intracellular signalling. To date, most work has focussed on blocking IGF action at the IGF1R. Antibody blockade inhibits mitogenic signalling by blocking ligand binding and enhancing receptor endocytosis. This can reduce growth of IGF2-secreting cancer cells (Lahm et al. 1994). However, IGF1R blockade may result in a compensatory increase in IR-A signalling, enabling cells to respond to IGF2 and become resistant to therapy (Belfiore et al. 2009, Gualberto & Pollak 2009, Garofalo et al. 2011). Prevention of autocrine IGF2 action, therefore, requires blockade of both receptors (Vella et al. 2002). Such simultaneous targeting of both IGF2 signalling routes has proven effective in osteosarcoma (Avnet et al. 2009). Recent work on GIST cell lines, expressing big IGF2 and IR-A, but not IGF1R, showed that cell survival was reduced when signalling was disrupted by down-regulation of big IGF2 or IR-A. Big IGF2/IR-A signalling is, therefore, a potential therapeutic target (Rikhot et al. 2012).

Targeting IGF2 itself could prevent its action through either receptor. First, antisense oligonucleotides could
potentially reduce IGF2 expression. Alternatively, IGF2 could be inactivated following its secretion. MABs that bind IGF2 inhibit IGF1R phosphorylation and growth of cancer cells (Feng et al. 2006, Gao et al. 2011) but have not yet been trialled in humans. Tumour gene therapies targeted at cells expressing IGF2 are another exciting recent development (Amit & Hochberg 2010, Pan et al. 2010). Vitamins C and D reduce IGF2 production and IGF1R signalling (Oh et al. 2001, Galbiati et al. 2003, Lee et al. 2008). There may be a place for combining these vitamins, or analogues thereof with other treatments. Releasing hormones have potential as therapeutic agents. GNRH reduced production of IGF2 in ovariectomised cancer and endometrial cancer cells resulting in reduced growth (Kleinman et al. 1993, Ho et al. 1997). Antagonists of GHRH also block IGF2 production by cancer cell lines inhibiting their growth (Csernus et al. 1999). In principle, IGF2 concentrations could be lowered by enhancing IGF2R-mediated clearance or by reducing IGF2 expression by epigenetic modification, although it is not yet known how to achieve this.

Given that components of the IGF system interact to determine IGF bioactivity, it is likely that approaches targeting multiple sites in the system will prove more effective than single-site approaches. Clinical trials will clarify whether inhibition of IGF2 signalling can prevent tumour growth in vivo in humans.

Future considerations

This is an exciting time in our understanding of IGF2. Knowledge of its role in disease is starting to suggest new diagnostic tests and therapeutic approaches. However, despite much research, the autocrine action of IGF2 in vivo is poorly understood, mainly because this cannot easily be measured. A challenge for the future will be to understand how IGF2 interacts with other components of the system at tissue level to influence cancer development and progression. Similarly, genetic and epigenetic changes affecting IGF2 need to be considered in the context of the whole genome.

While there has been abundant research into the disease association of IGF system components, future work needs to place a greater emphasis on the clinical value of measurement of these components, including IGF2, as diagnostic tests. In order to be adopted into the clinical repertoire, such tests will require to have demonstrable clinical utility and preferably also to be non-invasive and low cost. The expense and lack of availability of IGF2 assays in clinical laboratories has hindered clinical studies in the past, but this may change with the advent of its measurement by liquid chromatography mass spectrometry (Bystrom et al. 2012).

Cancer prevention is a promising area for future IGF2 research. The suggestion that in utero exposures predispose to cancer in adult life, in part through changes in IGF2 expression, raises the question of whether these exposures can be reduced, for example by periconceptual optimisation of parental body weight. This demands investigation by prospective studies. Studies also need to establish whether IGF2 predisposes to cancer in obesity and whether lowering its concentration reduces risk. If so, there may be a case for targeting individuals for risk reduction therapies.

Declaration of interest

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