

REVIEW

Signalling by insulin and IGF receptors: supporting acts and new players

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Abstract

The signalling pathways utilised by insulin receptor (IR) and IGF receptor to transduce their diverse effects on cellular metabolism, growth and survival are well established in broad outline, but many details remain to be elucidated. Tyrosine phosphorylation of IR substrates and Shc initiates signalling via canonical phosphoinositide 3-kinase/Akt and Ras/MAP kinase pathways, which together mediate many of the actions of insulin and IGFs. However, a variety of additional substrates and scaffolds have been described that may play roles in modulating the canonical pathways or in specific biological responses. This review will focus on recent studies that have extended our understanding of insulin/IGF signalling pathways, and the elements that may contribute to specificity.

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Introduction

Insulin and the insulin-like growth factors (IGFs) control many aspects of metabolism, growth and survival in a wide range of mammalian tissues (Nakae *et al.* 2001). Insulin/IGF signalling also contributes to regulation of lifespan (Narasimhan *et al.* 2009), while dysregulation of signalling has been implicated in neoplasia (Pollak 2008). Although insulin and IGFs play distinct physiological roles, they utilise the same signalling pathways, involving phosphoinositide 3-kinase (PI3K) and Akt or Ras and MAP kinase, which mediate responses to many other cellular stimuli. In large part, stimulus/response specificity must reflect the levels of expression of receptors and downstream targets in different tissues together with combinatorial effects (Dumont *et al.* 2002). However, it is widely assumed that specificity is also imparted by differences in ligand binding and intrinsic signalling capacities of the insulin and IGF receptors (IGFRs). This review focuses on recent advances in understanding receptor-proximal signalling mechanisms, including factors that may contribute to specificity of insulin and IGF action.

Receptors

The insulin receptor (IR) exists as two isoforms differing by the presence (IR-B) or absence (IR-A) of 12 amino acids at the carboxyl terminus of the

α -subunit, as a result of alternative splicing of the sequence encoded by exon 11. In the type 1 IGFR, the corresponding sequence is always lacking. IR-B is the more abundant isoform in muscle, liver and fat. Insulin binds with similar affinity to both isoforms, but IGFs, and particularly IGF2, have greater affinity for IR-A than IR-B such that IR-A is a significant mediator of IGF2 action at physiological concentrations. Some studies have indicated that IR-B may signal more efficiently to metabolic endpoints and IR-A to mitogenic endpoints (Belfiore *et al.* 2009). It has been suggested that IR isoforms localise to different lipid raft microdomains within which distinct signalling complexes are assembled (Leibiger *et al.* 2010a).

Additional complexity arises from hetero-dimerisation of pro-receptors, generating insulin/IGF hybrid receptors. Both IR isoforms can form hybrids with IGFR as well as with each other. Hetero-dimerisation occurs with similar efficiency to homo-dimerisation, so that if one receptor is expressed in excess, the less abundant is assembled largely into hybrids. Hybrids bind IGFs with similar affinity to IGFR, but bind insulin with substantially lower affinity than IR (Belfiore *et al.* 2009). It is unclear whether hybrid receptors have a distinct physiological role.

Receptor structure

The structure of the IR ectodomain explains many features of ligand binding (Lawrence *et al.* 2007).

Relative to the plasma membrane, the ectodomain has a folded-over conformation in which the two half-receptors lie anti-parallel and surround a ligand-binding pocket. The most significant structural differences between IR and IGFR are in the regions governing ligand specificity. Attempts to co-crystallise ligand–receptor complexes have been unsuccessful but other evidence indicates that high-affinity ligand binding involves contacts in *trans* with both half-receptors (De Meyts 2008). Despite the dimeric receptor structure, only a single molecule of ligand can make all the contacts required to bind with high affinity and binding therefore demonstrates negative cooperativity, fitting a harmonic oscillator model (Kiselyov *et al.* 2009). The contacts made by individual ligands and kinetics of ligand–receptor interaction may influence the extent, duration and perhaps even the nature of receptor activation. Specificity has been reported in the responses elicited by different ligands acting on the same receptor (Jensen & De Meyts 2009).

Receptor trafficking

As well as initiating intracellular signalling, ligand-induced autophosphorylation triggers internalisation of ligand/receptor complexes, leading to dissociation and degradation of ligand in the intracellular endosome/lysosome system and inactivation and recycling of receptors (Foti *et al.* 2004). However, receptor internalisation may also play an active role in signalling, particularly via the Ras/MAP kinase pathway to ‘mitogenic’ endpoints (Jensen & De Meyts 2009). Internalisation and recycling of IGFR may sustain IGF-induced Akt phosphorylation (Romanelli *et al.* 2007). More controversially, it has been reported that IR signalling complexes are recruited to specific insulin-inducible gene loci (Nelson *et al.* 2011) and that nuclear IGFR binds to chromatin and acts directly as a transcriptional enhancer (Aleksic *et al.* 2010, Sehat *et al.* 2010). Sumoylation may play a role in nuclear targeting of IGFR (Sehat *et al.* 2010), but the pathways by which active receptors could traffic to the nucleus are unclear.

Receptor regulation

Internalised receptors are inactivated by phosphotyrosine-specific phosphatases, particularly PTP1B, which is localised to the cytosolic face of the endoplasmic reticulum (Dube & Tremblay 2005). IR and IGFR function is regulated by a variety of mechanisms (Youngren 2007). The membrane glycoprotein PC-1, an ecto-nucleotide pyrophosphatase and phosphodiesterase, binds to the IR α -subunit and inhibits insulin-induced TK activity (Goldfine *et al.* 2008).

SOCS proteins induced by cytokine signalling inhibit tyrosine phosphorylation of IRSs through competition at the docking site on the IR (Lebrun & Van Obberghen 2008). The actions of Grb10 and Grb14 adaptors are potentially complex. It is not clear whether the expression and function of Grb10/14 are regulated or they act constitutively. Binding of Grb10/14 to autophosphorylated IR/IGFR (and some other RTKs) via their Src homology-2 (SH2) domains inhibits TK activity and IRS phosphorylation (Holt & Siddle 2005). However, Grb10/14 also protect phosphotyrosines in the TK regulatory loop from dephosphorylation, effectively prolonging receptor activation (Nouaille *et al.* 2006, Smith *et al.* 2007). Grb10 additionally promotes receptor degradation by recruitment of the ubiquitin ligase NEDD4 (Vecchione *et al.* 2003, Ramos *et al.* 2006), while both Grb10 and Grb14 recruit additional protein-binding partners with potential signalling roles (Holt & Siddle 2005). Gene deletion studies in mice confirm that Grb10 and Grb14 act as inhibitors of insulin signalling *in vivo*, with some specificity that probably reflects their different interactions and tissue distributions (Holt *et al.* 2009). Expression of the *Grb10* gene is imprinted from each of the parental alleles in a tissue-specific manner, and ablation of individual alleles has distinct effects on foetal growth (through maternal allele, widely expressed) and adult behaviour (through paternal allele, expressed in brain) which may not be dependent on insulin/IGF signalling (Garfield *et al.* 2011).

Canonical signalling pathways

The major signalling pathways by which IR and IGFR regulate metabolism and gene expression, with central roles for the serine kinases Akt/PKB and MEK kinase, are well established (Adams *et al.* 2004, Cohen 2006, Taniguchi *et al.* 2006, Laviola *et al.* 2007). Activation of these kinases is dependent on the phosphorylation of IR substrates (principally IRS1 and -2) and Shc, leading to activation of PI3K and the small G-protein Ras (Fig. 1).

PI3K/Akt pathway

IRSs are relatively specific substrates of IR/IGFR, reflecting the role of IRS phosphotyrosine binding (PTB) and pleckstrin homology (PH) domains in recruitment by these receptors (White 2002). IRS2 additionally interacts directly with the tyrosine kinase domains (Wu *et al.* 2008). Tyrosine phosphorylation of IRSs creates binding sites for SH2 domains of various proteins, notably the regulatory subunits of class Ia PI3Ks and the adaptor Grb2 and also the phosphatase SHP2 and the Src family kinase Fyn. The sequence

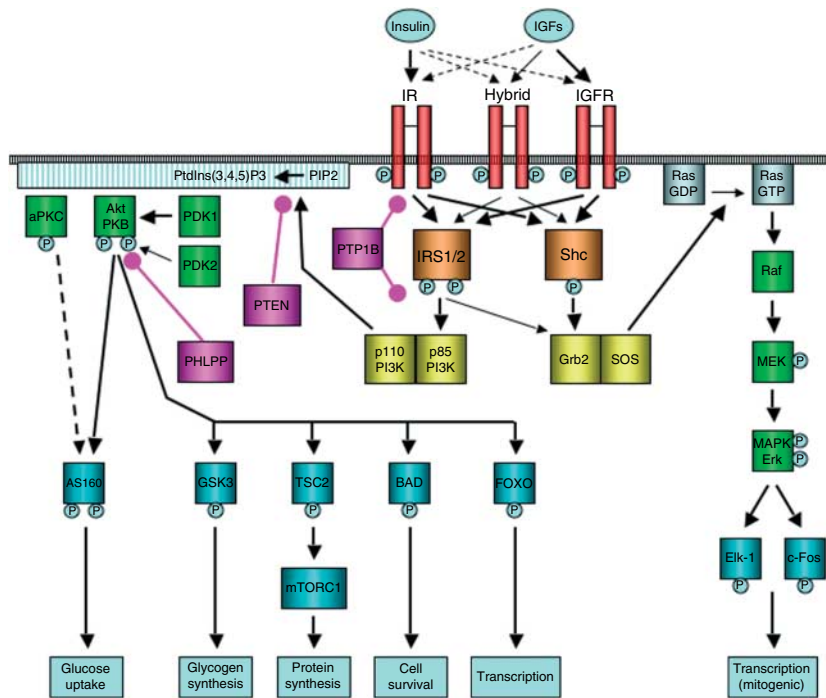


Figure 1 Canonical signalling pathways. The principal components of the PI3K/Akt and Ras/MAP kinase pathways are indicated: receptors (in red), tyrosine-phosphorylated substrates (in orange), adaptors and transducers (in yellow and grey), serine/threonine kinases (in green), serine/threonine phosphorylated substrates and downstream components (in blue) and negative regulators (in purple).

context of phosphotyrosines determines specificity of SH2 binding, the three residues immediately downstream being particularly important although such motifs do not fully explain selectivity (Liu *et al.* 2010). In terms of downstream signalling, IRS1 appears to be linked to glucose homeostasis and IRS2 to regulation of lipid metabolism (Taniguchi *et al.* 2005, Bouzakri *et al.* 2006, Thirone *et al.* 2006), though the mechanisms underlying this specificity are unclear. IRS1 and -2 recruit a similar spectrum of proteins including PI3Ks, although some differential interactions have been identified (Hanke & Mann 2009). Functional specificity might also arise from differences in the kinetics of phosphorylation or the subcellular localisation of IRSs.

IRSs are regulated by feedback mechanisms and crosstalk from other pathways. IRS1 is phosphorylated on multiple serine/threonine residues by kinases downstream in the insulin signalling pathway, including Akt/PKB, S6K1 and glycogen synthase kinase-3 (GSK3), and in other pathways, including AMPK, PKCs, Jnk and IKK β (Boura-Halfon & Zick 2009, Sun & Liu 2009). In general, serine/threonine phosphorylation inhibits IRS1 function (by promoting degradation, inhibiting interaction with IR/IGFR or inhibiting association of SH2 domains) although phosphorylation at certain

sites can potentiate IRS1 tyrosine phosphorylation. Serine phosphorylation of IRS2 has been less studied, but is likely to be equally complex (Fritsche *et al.* 2011). Subversion of physiological regulatory mechanisms by lipid metabolites, adipokines or inflammatory mediators is believed to contribute to insulin resistance associated with pathological states, including obesity (Boura-Halfon & Zick 2009, Sun & Liu 2009). However, insulin signalling can also be modulated by other mechanisms and at other sites downstream of IRSs (Taniguchi *et al.* 2006, Hoehn *et al.* 2008, Li *et al.* 2010). Such controls may be tissue specific and, because of the branching nature of insulin/IGF signalling pathways, selective in terms of the biological responses affected. Genome-wide scanning revealed multiple negative regulators of insulin signalling, including previously uncharacterised proteins as well as diverse phosphatases and kinases (Huang *et al.* 2009).

Reversible modification of protein serine/threonine residues also occurs by *O*-GlcNAcylation, and is thought to affect a large number of cytoplasmic and nuclear proteins. The modification potentially provides a mechanism of crosstalk with phosphorylation, regulating protein stability and subcellular localisation and protein-protein interactions (Zeidan & Hart 2010). Several components of insulin signalling pathways,

including IRS1, are transiently modified by *O*-GlcNAc following insulin stimulation, and this in turn modulates their serine phosphorylation and attenuates insulin signal transduction (Yang *et al.* 2008). IRS1 is *O*-GlcNAcylated at multiple sites in close proximity to SH2 domain-binding motifs (Klein *et al.* 2009), and pharmacological elevation of *O*-GlcNAcylation inhibits tyrosine phosphorylation of PI3K-binding motifs (Whelan *et al.* 2010). *O*-GlcNAcylation is a nutrient- and stress-sensitive modification, reflecting dependence on the hexosamine biosynthetic pathway, and it may contribute to diabetes-associated insulin resistance (Slawson *et al.* 2010).

Both IRS1 and -2 possess multiple tyrosines within YxxM motifs which, following phosphorylation, recruit the tandem SH2 domains of class Ia regulatory subunits (White 2002). Both regulatory and catalytic subunits of PI3Ks exist as multiple isoforms (p85 α /p55 α /p50 α , p85 β , p55 γ regulatory and p110 α , p110 β , p110 δ catalytic) that are the products of distinct genes diversified by alternative splicing (Shepherd *et al.* 1998). Regulatory and catalytic subunits appear to associate in all possible combinations, subject to their relative expression. Regulatory subunits are normally in excess, competing with active heterodimers for binding to IRSs and antagonising function by other mechanisms (Taniguchi *et al.* 2006). Several studies have suggested that insulin signals primarily via p110 α although the mechanism for such selectivity is unclear (Foukas *et al.* 2006, Knight *et al.* 2006, Sopsakis *et al.* 2010). However, other studies indicate roles for both p110 α and p110 β in insulin signalling, with evidence of functional redundancy or complementarity (Brachmann *et al.* 2005, Chaussade *et al.* 2007, Jia *et al.* 2008, Tups *et al.* 2010).

The lipid product of PI3Ks, PtdIns(3,4,5)P₃, induces the activation of protein serine kinase cascades by co-recruitment to membranes of phosphoinositide-dependent kinase-1 (PDK1) and its substrate kinases Akt/PKB and atypical protein kinase Cs (aPKCs), via their respective PH domains (Mora *et al.* 2004). PDK1 activates Akt/PKB and aPKC by phosphorylation of serine/threonine residues in their kinase regulatory loops (Pearce *et al.* 2010). Activation of Akt/PKB additionally requires phosphorylation of a C-terminal hydrophobic motif, catalysed by a distinct enzyme, most probably mTORC2 or DNA-PK (Bozulic & Hemmings 2009). The duration and amplitude of Akt signalling are controlled by PHLPP, a phosphatase that acts specifically on the hydrophobic phosphorylation motif (Brognard & Newton 2008).

Activated Akt/PKB phosphorylates multiple substrates and controls a variety of downstream responses depending on cell type (Manning & Cantley 2007, Vasudevan & Garraway 2010). In some cases, phosphorylation of targets itself regulates activity, while in

others binding of 14-3-3 protein also plays a role (Johnson *et al.* 2010). There are three isoforms of Akt/PKB encoded by distinct genes, and functional specificity of isoforms has been demonstrated in signalling to metabolism and growth (Dummler & Hemmings 2007, Gonzalez & McGraw 2009, Schultze *et al.* 2011). Well-established Akt/PKB substrates include GSK-3, regulating glycogen synthesis; the Rab GTPase activating protein AS160/TBC1D4, regulating glucose transport; the Rheb GTPase activating complex TSC1/2, regulating mTOR and protein synthesis; FOXO transcription factors, regulating expression of gluconeogenic and other genes; and BAD, regulating apoptosis (Manning & Cantley 2007, Vasudevan & Garraway 2010). Both Akt-dependent and -independent mechanisms have been implicated in regulation of adipose tissue lipolysis by insulin (Berggreen *et al.* 2009, Choi *et al.* 2010). The precise functions of aPKCs are less understood (Hirai & Chida 2003, Rosse *et al.* 2010).

Enzymatic and proteomic techniques (Cohen & Knebel 2006, Choudhary & Mann 2010) and bioinformatic tools (Miller & Blom 2009) have been developed for the discovery and prediction of cellular substrates of Akt/PKB and other kinases. However, identification of potential Akt substrates has outstripped their validation as important physiological targets (Manning & Cantley 2007). The problem is well illustrated by the finding that allosteric regulation of glycogen synthase by glucose 6-phosphate, rather than covalent regulation by the Akt/GSK-3 cascade, is the major mechanism by which insulin stimulates muscle glycogen synthesis *in vivo* (Bouskila *et al.* 2010).

Activation of Akt/PKB mediates insulin-stimulated translocation of GLUT4 glucose transporters in muscle and adipose tissue (Whiteman *et al.* 2002), although aPKC ζ / λ can apparently play a similar role (Farese & Sajan 2010). Whether activation of either kinase is sufficient for a maximum response is less clear and additional mechanisms may also be required. These include actin remodelling mediated by activation of Rho family GTPases such as TC10 (Chang *et al.* 2004) and Rac1 (Ishikura *et al.* 2008). It is likely that regulation is exerted at multiple steps of GLUT4 traffic, including the release or budding of vesicles from their storage pool, movement to and docking with the plasma membrane and fusion with the plasma membrane (Watson & Pessin 2007, Larance *et al.* 2008). The Akt/PKB substrate AS160/TBC1D4, whose Rab GAP activity is inhibited by insulin-induced phosphorylation, has emerged as a key component of regulation of GLUT4 traffic although its site of action is uncertain (Sakamoto & Holman 2008, Chen *et al.* 2011). The Rabs and their effectors that are activated as a consequence of AS160 phosphorylation have yet to be conclusively identified (Sano *et al.* 2008).

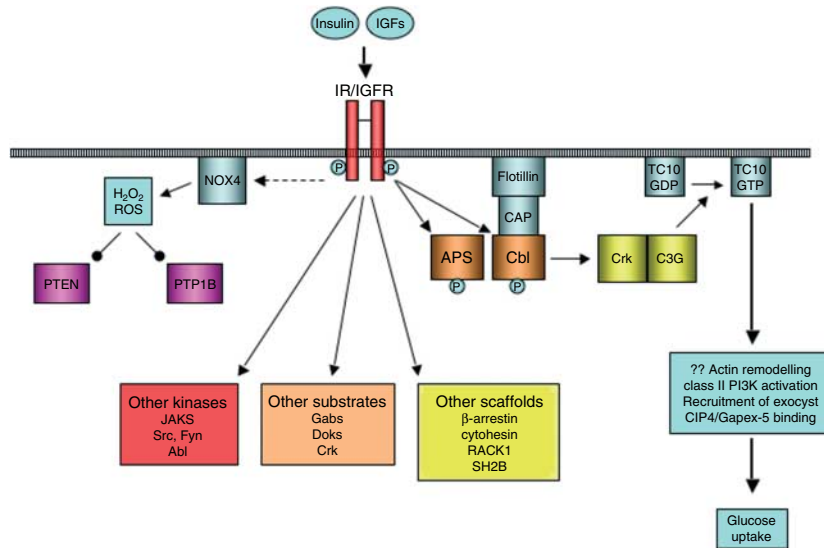


Figure 2 Additional pathways and components. Some accessory components of insulin/IGF signalling pathways are indicated: tyrosine kinases (in red), tyrosine-phosphorylated substrates (in orange), adaptors and transducers (in yellow and grey) and negative regulators (in purple).

Ras/MAP kinase pathway

In common with many receptor tyrosine kinases, IR and IGFR regulate cell growth-related gene expression via the Ras/MAP kinase pathway (Avruch 2007). The pathway is initiated by recruitment of the adaptor/guanine nucleotide exchange factor complex Grb2/Sos to phosphorylated Shc and/or IRSs. It is unclear whether Shc-bound and IRS-bound Grb2/Sos complexes are equally effective activators of Ras, given the differences in their abundance, subcellular localisation and potential co-recruitment of additional components. In some cells, Shc is the more important substrate for Ras/MAP kinase activation (Pruett *et al.* 1995), while in others, IRS-dependent pathways appear to predominate (Takahashi *et al.* 1997). Shc and IRSs may compete in binding to IR/IGFR and in recruiting a limited pool of Grb2, and this could influence signalling to ‘metabolic’ versus ‘mitogenic’ responses (Sasaoka *et al.* 2001).

Activation of Ras by Sos depends on mutual proximity and relief of Sos autoinhibition (Gureasko *et al.* 2008). Activated (GTP-bound) Ras in turn activates the kinase Raf, the dual specificity kinase MEK, MAP kinase/ERK and further downstream kinases (Ramos 2008). Scaffold proteins play a role in co-ordinating this cascade, and may influence cellular responses through effects on signal intensity and duration, localisation of complexes and recruitment of modulatory proteins such as phosphatases and ubiquitin ligases (Brown & Sacks 2009). Functional differences between isoforms of MAP kinase (ERK1/2) and MAP kinase (MEK1/2)

have been discussed in relation to cell cycle regulation (Sturgill 2008).

Additional pathways

Various accessory pathways, kinases, adaptor proteins and scaffolds have been implicated in modulating IR/IGFR signalling via PI3K/Akt and Ras/MAP kinase pathways (Fig. 2).

Redox: PTPs and PTEN

Evidence from cellular studies indicates that activation of IR/IGFR (and certain other RTKs) promotes generation of reactive oxygen and nitrogen species, which inhibit protein and lipid phosphatases including PTP1B and PTEN by reversible modification of active-site cysteine residues, and thereby potentiate the effects of tyrosine phosphorylation and PI3K activation (Goldstein *et al.* 2005, Vardatsikos *et al.* 2009, Hsu & Meng 2010). The NAD(P)H oxidase homologue Nox4 has been identified as a likely source of insulin/IGF-stimulated H₂O₂ generation (Goldstein *et al.* 2005, Meng *et al.* 2008) but the mechanisms coupling IR/IGFR signalling to Nox4 activation remain obscure. Evidence from mouse knockout models confirms that reactive oxygen species enhance insulin sensitivity *in vivo* (Loh *et al.* 2009), although chronic oxidative stress contributes to the development of insulin resistance and diabetic complications (Cheng *et al.* 2010, Giacco & Brownlee 2010).

CAP/Cbl pathway: IR and glucose uptake

It has been proposed that stimulation of glucose transport by insulin involves a second pathway in addition to PI3K/Akt. This Cbl-associated protein (CAP)/Cbl pathway is initiated by tyrosine phosphorylation of the adaptors APS and c-Cbl (Ahn *et al.* 2004, Hu & Hubbard 2005), leading to assembly of a signalling complex that is localised to lipid rafts by CAP and resulting in activation of TC10, a member of the Rho family of small GTPases (Chang *et al.* 2004). Effector mechanisms that might link TC10 to glucose transport include actin remodelling, assembly of exocyst complexes and generation of PtdIns3P (Chang *et al.* 2004, Falasca *et al.* 2007). However, the physiological importance of the CAP/Cbl pathway in IR/IGFR function is uncertain. The pathway does not appear to operate in skeletal muscle (JeBailey *et al.* 2004), knockdown of key components does not disrupt insulin-stimulated glucose transport in adipocytes (Mitra *et al.* 2004) and knockout of APS or c-Cbl in mice actually improves peripheral insulin sensitivity (Minami *et al.* 2003, Molero *et al.* 2004, Li *et al.* 2006).

Other phosphoinositides: class II and III PI3Ks, PIKfyve

In addition to the well-established roles of class Ia PI3Ks, class II and class III PI3Ks and PIKfyve may play roles in signalling (Shisheva 2008a, Falasca & Maffucci 2009). Class II PI3Ks, whose *in vivo* product is PtdIns3P, have been implicated in regulation of glucose transport in muscle (Falasca *et al.* 2007) and gene expression in pancreatic β -cells (Leibiger *et al.* 2010b). PIKfyve, which synthesises PtdIns5P and PtdIns(3,5)P₂ and binds to PtdIns3P via its fyve domain, is phosphorylated by Akt and may be involved in GLUT4 translocation (Berwick *et al.* 2004). Dysfunction of PIKfyve produces endosome enlargement and cytoplasmic vacuolation (Shisheva 2008b), suggesting a general role in maintaining subcellular membrane compartments rather than a specific role in insulin signalling.

Other potential signalling components

It is outside the scope of this brief review to consider in detail other proteins that may play roles in insulin/IGF action, many of them more closely associated with other signalling pathways. However, in addition to IRSs, Shc, APS and c-Cbl discussed above, Gabs (Nishida & Hirano 2003) and DOKs (Mashima *et al.* 2009) are substrates for IR and IGFR tyrosine kinases. Insulin and IGFs have been reported to activate non-receptor TKs, including JAKs (Himpe & Kooijman 2009), Src family kinases (Bromann *et al.* 2004) and

c-Abl (Sirvent *et al.* 2008). Other proteins implicated in actions of insulin or IGFs include SH2-B (an adaptor protein related to APS) (Duan *et al.* 2004, Li *et al.* 2006, Morris *et al.* 2009), cytohesins (guanine nucleotide exchange factors for ARF family GTPases; Fuss *et al.* 2006, Hafner *et al.* 2006), the scaffold CNK1 (Lim *et al.* 2010), the WD repeat protein RACK1 (Kiely *et al.* 2008, 2009) and β -arrestins (Luan *et al.* 2009). The mechanisms of involvement of these proteins in insulin/IGF signalling pathways are largely speculative and require further study.

Conclusion

Many details of insulin/IGF signalling remain to be clarified, including the specific roles of receptor isoforms and hybrid receptors; the role of accessory pathways, kinases and scaffolds in modulating or supplementing canonical PI3K/Akt and Ras/MAP kinase pathways; the precise mechanisms underlying the regulated trafficking of GLUT4 glucose transporters; and the feedback and crosstalk mechanisms that modulate signalling under different physiological and pathological conditions. In relation to the long-standing issue of insulin/IGF signalling specificity, recent studies suggest that 'IR and IGFR act as identical portals for the regulation of gene expression, with differences between insulin and IGF1 effects due to a modulation of the amplitude of the signal created by the specific ligand-receptor interaction' (Boucher *et al.* 2010). However, mechanisms that might impart a degree of specificity to insulin and IGF responses are still being actively considered, focused largely on the influence of ligand-binding mechanism and kinetics (Jensen & De Meyts 2009). In spite of the wealth of information that has accumulated concerning IR and IGFR signalling pathways in the 25 years since the receptors were cloned, the precise nature and even the very existence of receptor-specific signalling mechanisms remain enigmatic.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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