Insulin and IGF-1 receptor signalling pathways: where is the specificity?

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The insulin receptor (IR) and the IGF-I receptor (IGF-IR) utilize common signalling pathways to mediate a broad spectrum of "metabolic" and "mitogenic" responses (1 - 5).

This signalling network is also engaged by other receptor tyrosine kinases (RTKs) (6).

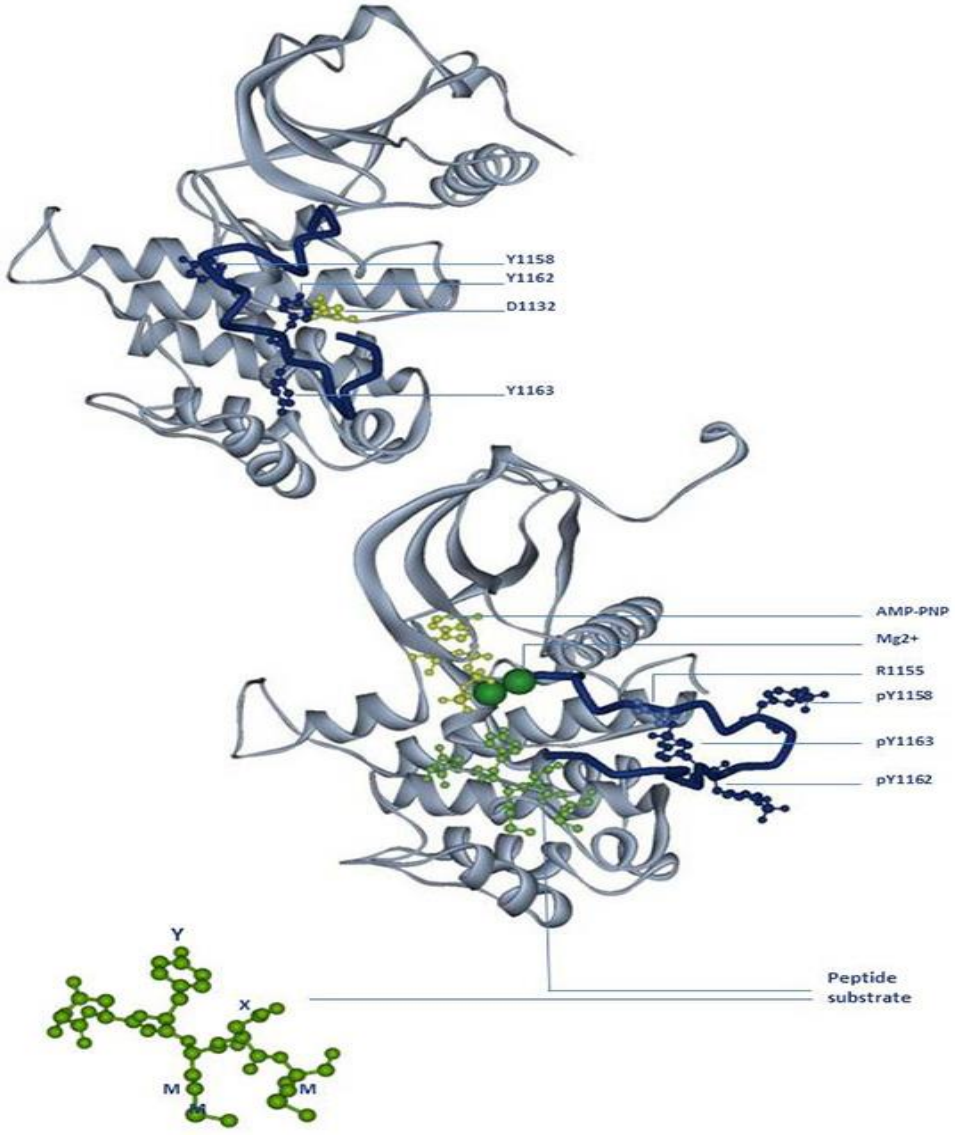
That insulin and IGF-I receptors have distinct physiological functions is exemplified by the distinct phenotypes of IR versus IGF-IR knockout (KO) mice (7). IR KO mice are born with almost normal size but die within a few days from acute ketoacidosis, while IGF-IR KO mice are born small and die quickly from asphyxia due to underdevelopment of thoracic muscles. This downstream specificity is not inherent to the receptor structures since it has been shown that the IR and the IGF-IR can exert each other's function in cases where the other receptor is absent. Thus, the IGF-IR can induce stimulation of glucose transport and glycogen synthesis, typical insulin metabolic effects, in fibroblasts from IR KO mice (8). Reciprocally, the IR stimulates thymidine incorporation and cell growth in a T-cell lymphoma line devoid of IGF-I receptors (9). There is therefore a paradox in having specific biological endpoints through ligand-specific receptors while the downstream signalling networks appear to be largely overlapping (1,10,11). There is currently no precise solution to this conundrum, except to state that the cellular context and the differential "combinatorial" use of the components of a common network, rather than intrinsic receptor activity, appear to be major determinants of biological "mitogenic" versus "metabolic" endpoints (1, 10, 11). A system biology approach to the modelling of complex signalling networks appears to be the way of the future in order to unravel this complexity.

A detailed description of the IR and IGF-IR signalling network is beyond the scope of this brief review, see refs. 1-5 for further reading.

Like other receptor tyrosine kinases, the IR and IGF-IR are activated upon ligand binding by transphosphorylation of specific tyrosyle residues in the inhibitory loop of the kinase domain (Fig. 1), making the loop move out of the active site (12).

Figure 1: Mechanism of insulin receptor tyrosine kinase (IRTK) activation. The X-ray structures of the inactive (left, PDB file 1IRK)) and activated (right, PDB file 1IR3) IRTK are shown. The activated structure on the right is bound to an ATP analogue,

adenylyl imidodiphosphate (AMP-PNP) as well as a peptide substrate YMXM and magnesium. The figure illustrates the autoinhibition mechanism, whereby Tyr (Y) 1162 - one of the three tyrosines (Y1158, Y1162 and Y1163) that are autophosphorylated in the activation loop (in white) in response to insulin - is bound in the active site, hydrogen-bonded to a conserved Asp (D) 1132 residue in the catalytic loop (a). Y1162 in effect competes with protein substrates before autophosphorylation. In the activated state (b), the activation loop is tris-phosphorylated and moves out of the active site. Y1163 becomes hydrogen-bonded to a conserved R1155 residue in the beginning of the activation loop, which stabilizes the repositioned loop. From ref. 28, adapted from ref. 16.



Unlike other RTKs, the IR and IGF-IR intracellular domains do not engage directly SH2 domain-containing signalling elements of the downstream cascades, but bind through a phosphorylated tyrosyle in the juxtamembrane domain a variety of docking proteins that get phosphorylated at multiple SH2-domain binding sites (1-4). These docking proteins comprise among others IRS-1, -2 -3- and -4 (13), Shc (14), Gab1 and Cbl.

The two main canonical signalling pathways engaged by both IR and IGF-IR are the phosphoinositide 3-kinase pathway (PI3K)/Akt (15) and Ras/extracellular signal-regulated kinase (ERK or MAPK) (16) pathways (Fig. 2). The PI3K/Akt pathway appears to be involved in metabolic events such as GLUT4 translocation, but also in mitogenic events in cooperation with the ERK pathway.

Below animation shows the intracellular signalling pathways of insulin and IGF-I receptors.

The main signalling pathways activated by insulin and IGF-I (the MAP kinase or MEK cascade on the right, the PI 3-kinase on the left) are shown together with their main biological end-points.

Abbreviations:
IRS: Insulin receptor substrate.
SHC: Src homology 2-containing protein.
Grb2: Growth factor receptor-bound protein 2.
SOS: Son of Sevenless.
Ras: A small GTPase, named after Rat Sarcoma.
RAF: Not an abbreviation, a MAP kinase kinase kinase.
MEK: MAP kinase/ERK kinase, MAP kinase kinase.
ERK: Extracellular signal-regulated kinase.
P90 RSK: Ribosomal Protein S6 kinase.
PI3K: Phosphatidylinositol 3- kinase.
PIP2: Phosphatidylinositol 3,4 bisphosphate.
PIP3: Phosphatidylinositol 3,4,5 trisphosphate.
PDK: 3-phosphoinositide - dependent protein kinase.

Akt: Not an abbreviation. = Protein kinase B (PKB).

FOXO: Forkhead box O.

mTOR: Mammalian target of rapamycin.

GLUT4. Glucose transporter 4.

PTP1B: Protein tyrosine phosphatase 1B.

PTEN: Phosphatase and tensin homologue deleted on chromosome 10.

GSK3: Glycogen synthase kinase-3.

Other notable elements of the downstream signalling pathways are FoxO1 (a transcription factor downstream of Akt that is involved in cell cycle regulation, oxidative stress resistance, apoptosis and metabolism e.g. gluconeogenesis (17)) and mTOR (downstream of Akt) and p90RSK (downstream of ERK), that together regulate protein synthesis (3).

Negative regulation of IR and IGF-IR signalling occurs through phosphatases such as PTP1B, SOCS proteins, serine phosphorylation of IRS proteins and receptor downregulation/endocytosis, as well as negative regulation of PI3K by the phosphatase PTEN (3).

In summary, while physiologically insulin is more a metabolic hormone and IGFs are growth factors, both receptors are intrinsically capable of mitogenic and metabolic signalling, through largely overlapping signalling networks. The molecular basis of their signalling specificity is still poorly understood. However it is clear that at high concentrations insulin can perfectly substitute for IGF-I in cell culture through the IGF-IR, as well as mediating some mitogenic effects through its own receptor.

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