

Research Highlight

How distinct hormones sculpt a common receptor: ligand-specific conformational pathways of the insulin receptor

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The insulin receptor (IR) lies at the heart of metabolic regulation, integrating hormonal cues to coordinate glucose uptake, lipid metabolism, growth, and survival [1–3]. While insulin is its canonical ligand, the insulin receptor also responds, albeit with lower affinity, to the insulin-like growth factors IGF-I and IGF-II. This cross-reactivity is physiologically relevant during development and tissue growth, and pathologically important in cancer, where the IR-A isoform and IGF-II signaling are frequently upregulated [4]. Despite decades of biochemical and structural investigation, a central question has remained unresolved: how do distinct hormones engage the same receptor yet elicit different modes of activation and downstream signaling [4,5]?

In this study, Yan and colleagues [6] provide a comprehensive structural answer by determining the first cryo-electron microscopy (cryo-EM) structures of full-length human IR-A bound to IGF-I, alongside those with insulin and IGF-II, under matched experimental conditions. By capturing multiple ligand-occupancy and conformational states for each hormone, the authors show that insulin and IGFs do not simply differ in binding affinity. Instead, they drive distinct conformational trajectories through a shared architectural framework, reframing IR activation as a ligand-dependent conformational selection process rather than a uniform on-off switch [7].

A Conserved Endpoint Reached by Divergent Paths

The insulin receptor is a disulfide-linked ($\alpha\beta$)₂ homodimer whose extracellular domain (ECD) adopts a folded, autoinhibited Λ -shaped conformation in the absence of ligand (Figure 1) [8]. Previous cryo-EM studies established that insulin binding induces large-scale rearrangements of the ECD, culminating in a symmetric T-shaped assembly that positions the transmembrane domains to enable kinase activation. This T-shaped conformation has generally been viewed as the fully active receptor state.

A striking finding of the present study is that insulin, IGF-I, and IGF-II can all induce a similar T-shaped quaternary organization, with up to four ligands occupying site-1/1' and site-2/2' across the IR dimer [7,8]. This demonstrates that the receptor's structural

endpoint is largely conserved, regardless of ligand identity. Importantly, however, this apparent similarity conceals profound differences in how each hormone reaches that endpoint.

By systematically varying ligand concentrations and classifying thousands of particles, the authors captured a continuum of intermediate conformations that reveal hormone-specific patterns of binding order, local flexibility, and domain rearrangement in these intermediate states. These intermediate states, rather than the final T-shaped assembly alone, encode the functional distinctions between insulin- and IGFs-mediated receptor activation.

Insulin: Rapid Stabilization through High-Affinity Locking

Insulin exhibits the highest affinity for IR, a property long attributed to its optimized interactions at binding site 1, formed by the L1 domain, the α -CT' helix, and the FnIII-1' domain (Figure 1) [7,9]. Consistent with this, the cryo-EM structures show that even at relatively low ligand occupancy, insulin robustly stabilizes the receptor head region. Across one-, two-, and four-insulin-bound states, the relative positions of the L1, CR, L2, and FnIII-1 domains remain remarkably similar, indicating that insulin rapidly “locks” critical structural elements into place.

As a consequence, insulin binding minimizes conformational heterogeneity, promoting synchronized activation across the receptor dimer and facilitating efficient signal transmission across the membrane by constraining movements of the membrane-proximal FnIII-2 and FnIII-3 domains. Together, these features provide a structural explanation for the fast, concentration-dependent activation of IR by insulin, a property that aligns precisely with the physiological demands of glucose homeostasis, where rapid and tightly controlled responses are essential.

IGF-I and IGF-II: Flexible Engagement and Sustained Activation

In contrast, IGF-I and IGF-II induce a markedly different activation landscape. Although both ligands ultimately support formation of the T-shaped assembly (with the symmetric IGF-II-bound state

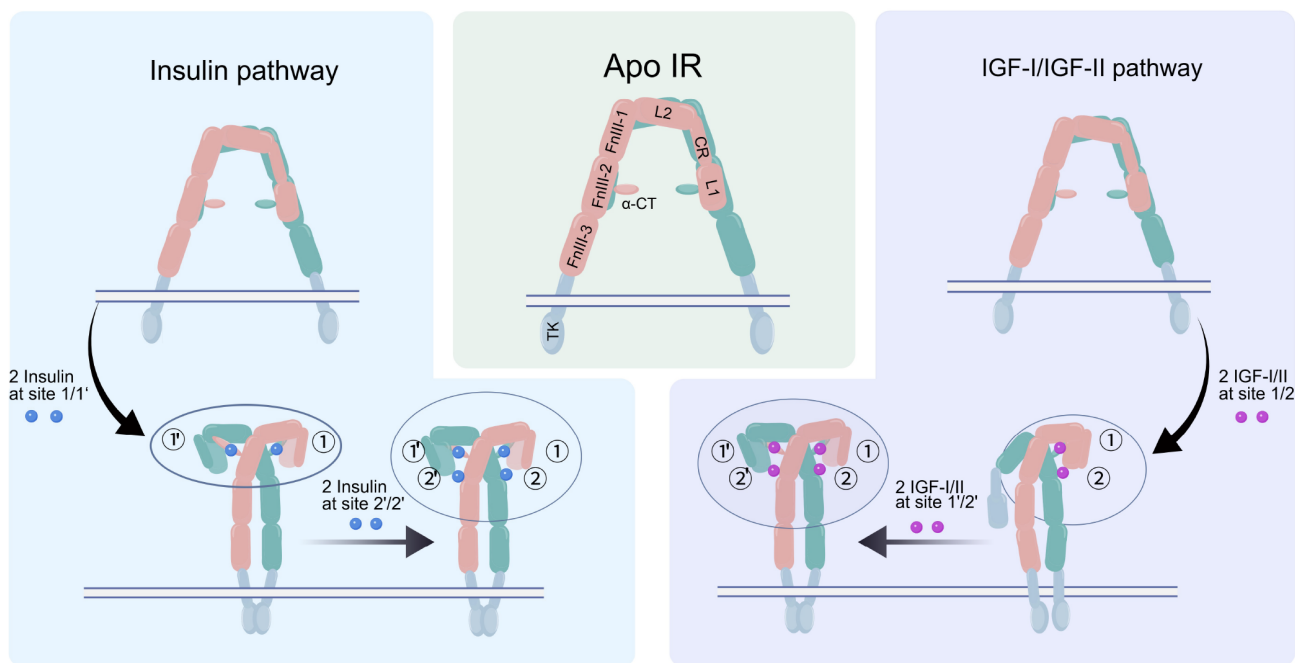


Figure 1. Distinct binding and activation modes of the insulin receptor Schematic illustration of the apo insulin receptor (IR) and models of IR activation upon binding insulin or insulin-like growth factors (IGF-I/IGF-II). Insulin is shown as brown spheres, IGF-I/IGF-II as purple spheres, and the two IR protomers are colored green and pink. Insulin preferentially engages site 1/1' and promotes a more symmetric receptor closure, whereas IGF-I/IGF-II bind across site 1/2 and site 1'/2', resulting in a distinct, asymmetric activation mode. Figure was generated using BioGDP (Generic Diagramming Platform) [10].

resolved at lower resolution), their binding is characterized by greater conformational plasticity and a pronounced preference for asymmetric intermediate states, particularly in the case of IGF-I (Figure 1). Across a wide range of ligand concentrations, IGF-bound receptors populate conformations in which ligands occupy site 1 and site 2 on a single protomer, while the opposing protomer remains partially unengaged [4,8].

These asymmetric states are not transient anomalies but dominant populations. Structurally, they are associated with increased flexibility in the FnIII-1, FnIII-2, and FnIII-3 domains, together with local rearrangements of the α -CT helix. Rather than rapidly locking the receptor into a rigid configuration, IGFs appear to promote dynamic sampling of multiple conformations before achieving full occupancy.

This flexible engagement mode offers a compelling structural rationale for the biological behavior of IGFs. Unlike insulin, which is secreted in sharp pulses, IGF-I and IGF-II circulate at relatively stable levels. A receptor activation mechanism that favors sustained and adaptable engagement over abrupt switching is therefore well suited to mediating long-term processes such as growth, differentiation, and tissue remodeling.

Site-Specific Recognition and Cooperative Binding

At the molecular level, detailed analysis of binding site 1 reveals both conserved and ligand-specific features. Core residues from the L1 domain and α -CT' helix, including Asn42, Glu738, and Arg744, participate in binding all three hormones, underscoring a shared recognition strategy. However, insulin forms a denser network of hydrogen bonds at site 1, consistent with its higher affinity and

stabilizing effect. By contrast, IGF-I and IGF-II engage site 1 in subtly different orientations and rely more heavily on interactions at site 2 and site 1'.

This differential weighting of binding sites provides a structural basis for earlier biochemical observations of ligand-specific cooperativity and negative cooperativity within the IR. In particular, the data suggest that IGFs engage secondary sites more efficiently than insulin, facilitating multi-ligand occupancy despite lower overall affinity [9,11,12].

Collectively, these findings indicate that IR activation is governed not simply by how tightly a ligand binds, but by which sites it favors, in what sequence, and with what impact on local flexibility—features that are invisible in static endpoint structures but become evident through the comparative, multi-state approach employed here.

Implications for Signaling Specificity, Disease, and Therapeutic Innovation

Although the present study focuses on the extracellular domain, its implications extend directly to intracellular signaling. Distinct ECD conformations are expected to impose different geometric constraints on the transmembrane and kinase domains, thereby influencing autophosphorylation patterns and downstream adaptor recruitment. The flexible, asymmetric states favored by IGFs may underlie the well-documented bias of IGF signaling toward mitogenic pathways, whereas insulin's rapid stabilization of a symmetric active state supports robust metabolic signaling.

These insights are particularly relevant in pathological contexts such as cancer, where IR-A is highly expressed in fetal tissues and

many tumors, with IGF-II serving as a potent autocrine ligand [8,11,13]. The structural capacity of IR-A to accommodate IGF-II in multiple configurations, and to form fully occupied assemblies with relative ease, provides a mechanistic foundation for aberrant growth signaling [11,12].

Beyond its immediate biological implications, this work establishes a conceptual framework for therapeutic innovation. Rather than targeting ligand binding per se, future strategies may aim to stabilize or destabilize specific conformational pathways of the insulin receptor. By selectively favoring insulin-like or IGF-like activation trajectories, it may be possible to decouple metabolic control from unwanted mitogenic effects, a long-standing goal in the treatment of diabetes and cancer.

Conclusion

Yan and colleagues [6] reveal that insulin and IGFs do not simply compete for occupancy of the insulin receptor, but instead sculpt its conformational landscape in ligand-specific ways. By elucidating how distinct hormones navigate divergent structural routes to a common endpoint, this study elevates our understanding of IR activation from static snapshots to dynamic pathways. More broadly, it illustrates how receptor tyrosine kinases can encode ligand specificity not through distinct binding sites, but through ligand-dependent navigation of a shared conformational landscape.

Conflict of Interest

The authors declare that they have no conflict of interest.

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