

P005 IGF-1 receptor and insulin receptor: how different are their catalytic domains?

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The receptors for insulin and IGF-1 are highly homologous but their activation by the respective hormones causes different cellular responses. To investigate to which extent the kinase domains could contribute to the signalling specificity, the core kinases of the insulin (IRKD) and the IGF-1 receptor (IGF-1RKD) were expressed via the Baculovirus system and tested for their catalytic activity in autophosphorylation and substrate phosphorylation. Autophosphorylation of both constructs is concentration dependent as expected for a trans-reaction. In substrate phosphorylation both of them show a low k_{cat} and a high $K_{m_{ATP}}$ in the basal state and upon autophosphorylation a ≥ 10 fold increase in k_{cat} and decrease in $K_{m_{ATP}}$, respectively.

However, we find basic differences between the two kinase constructs: Dimerisation ability of IGF-1RKD is significantly weaker than of IRKD and both kinase domains also markedly differ in the ATP-dependency of autophosphorylation. Limited proteolysis reveals, however, that there is no difference in the accessibility of the nucleotide binding site.

Comparison of the known structures of both kinase domains makes it likely that the observed differences can be accredited to the truncated N-terminus of the constructs. Thus, comparison of IGF-1RKD and IRKD reveals unique characteristics in ATP-binding and dimerisation interfaces which could be important for the development of kinase specific drugs.