Oral Contributions

[MS5] Structure and function of biomacromolecules

Co-Chairs: Marjolein Thunnissen (SE), Gerlind Sulzenbacher (FR)

[MS5-01] First Structural Insights Into Insulin - Insulin Receptor Complex. Andrzej Marek Brzozowski,

York Structural Biology Laboratory, Dept. of Chemistry, University of York, York YO10 5DD, U.K.,
E-mail: marek.brzozowski@york.ac.uk

Human insulin is a 51-amino acid hormone that regulates blood glucose levels, lipid/protein metabolism, and is also involved in modulation of the life span. Insulin exerts its actions through binding as a monomer to the 450 kDa $(\alpha\beta)_2$-homodimeric, tyrosine kinase-type insulin receptor (IR).
Insulin consists of A-chain (GlyA1-AsnA21) and B-chain (PheB1-ThrB30) that are linked by two interchain disulphide bridges. Insulin dimerise at low micro molar concentrations, and the presence of divalent metal ions such as Zn^{2+} leads to the formation of insulin hexamers that represent the storage form of this hormone. There is overwhelming evidence that monomeric insulin must undergo structural changes upon binding to IR. Mainly, the C-terminal ~B22-B30 part of the B-chain has to rearrange to reveal amino acids that are crucial for an effective formation of the hormone-receptor interface and which are obstructed by C-terminal B22-B30 β-strand in the dimeric and hexameric forms of the hormone. Since the first 3-D description of insulin structure by Dorothy Hodgkin group in 1969 [1] the understanding of insulin binding to IR was based mostly on the inactive, storage (hexamers, dimers) states of the hormone, or its engineered monomers [2]. The structures of some ectodmain constructs of the IR have been determined, but only in their *apo*-forms [3]. Recently, an extensive and interdisciplinary collaborative effort provided the first insight into the mode of insulin binding to IR [4]. This work was focused on IR α-subunit fragments containing L1-CR-L2-FnIII-1 (IR593.αCT) and L1-CR (IR310.T) domains that cover the key hormone binding sites. Several complexes with wild type and high affinity insulins have been determined. The α-subunit 15-amino acid C-terminal segment (αCT) was crucial for an effective hormone binding. All insulin-IR complexes showed the same mode of hormone-receptor interaction. Most remarkably, they revealed that the direct contacts of insulin with the L1 IR domain are rather sparse. Instead, the hormone is engaged with the receptor via the αCT segment that is anchored on the surface of the L1 domain formed by its central β-sheet. Most of the insulin side chains involved in this interactions form so-called insulin site 1. The observed insulin:IR binding mode unifies plethora of various biochemical and biophysical data and rationalizes long-standing anomalies in some diabetes-related insulin variants. It also confirms the 'induced-fit' of insulin on the IR surface during complex formation that requires the displacement of the insulin B26¬B30 chain upon binding to the receptor; although the B21-B30 cannot be seen in the complexes, the wild type conformation of these residues would clash with the αCT-segment indicating the need for reallocation of the B26-B30 part of the hormone.
This work has been expanded now to *Drosophila* insulins that are highly homologous to human hormone. They represent a workable system to study complex structure-function-phenotype relationships within insulin-IGF family of hormones.

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[3]. McKern, N. M. *et al.* Structure of the insulin receptor ectodomain reveals a folded-over conformation. *Nature*, **443**, 218–221 (2006)
[4]. Menting, J.G., *et al.* & Lawrence M.C. How insulin engages its primary binding site on the insulin receptor. *Nature*, **493**, 241-245 (2013)

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