ABOUT SOME LIMITS IN STRUCTURAL BIOLOGY: TWO FACES OF HORMONE REGULATION

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Structural biology continues to be a source of ground-breaking advances in bioscience research. However, there are still many methodological barriers that limit applications of bio-crystallography and NMR and restrict progress in the understanding of cellular functions. Some of these challenges will be discussed here using two examples derived from studies on hormone regulation.

(i) Advances in the field of nuclear receptors (NR) have resulted in many structures of DNA- and Ligand-Binding Domains (LBDs) of these transcription factors. For example, several ligand-bound complexes of the Estrogen Receptor (ER) LBD have been solved, providing a clear 3-D description of the ER pharmacophore. Due to the different nature of ligands used in this research, they also provided considerable insight into mechanism of agonism, partial agonism/antagonism and full antagonism in the ER. As the ER LBD shares a canonical fold with corresponding domains of other NRs, some generalisation about the nature of agonism and antagonism across the whole family of human ligand-induced transcription factors is possible. However, the design of drugs based on oestradiol (and other small, lipophilic hormones) with controllable and desired tissue actions have been hampered by a lack of expansion of structural research into binary and tertiary complexes of NRs with their co-activators and co-repressors. In addition, the structure of a full length NR still eludes the best efforts of structural biologists.

(ii) The complex of insulin with its cognate Insulin Receptor (IR) is a Holy Grail of diabetes and insulin signalling research. Hundreds of insulin structures provided deep insight into the structure-function relationship of this hormone, however, the active form of this polypeptide that is adopted upon binding to IR is still unknown. On the other hand, several structures of the ectodomain of IR are now available but they present only the hormone-free conformation of this part of the IR; again the efforts to achieve a stable insulin-IR complex for structural studies were so far unsuccessful. The understanding of the nature of insulin-based hormone regulation is complicated further by its close structural similarity to IGF-1, which binds to IGF-1 Receptor, IR (with low affinity) and IGF-Binding Proteins that regulate bio-availability of this hormone. It also seems that 3-D forms of insulin and their corresponding functions can only be fully understood in the context of IGF-1 and insulin/IGF-related hormones in Drosphila, *C. elegans* and Hydra. Hence broad structural studies that can explain the origins of metabolic and growth factor properties of this family of hormones are necessary.