Protein vs. DNA: The tolerant gives in

Protein-Protein and Protein-DNA Interaction in Hormone Receptors

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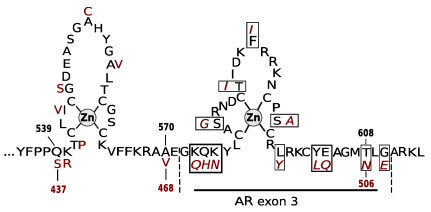
Kurzgefasst

- Hormon receptors bind to a specific DNA Sequence
- Flanking bases affect glucocortoid receptor conformation on DNA
- How are protein-protein and protein-DNA interaction balanced?

Hormon receptors play an eminent role in gene regulation. These receptors are proteins which consust of essentially three domains : the N-terminal domain, the ligand-binding domain which recognises and binds the hormon, and a DNA binding domain. The latter is very similar in different hormon receptor proteins.



Direct Repeat (DR): CC**AGAACA**tca**AGAACA**G
Invert Repeat (IR): CC**AGAACA**tca**TGTTCT**G

***Abbildung 1:** The androgen receptor binds DNA sequences with inverted and with direct repeat, the glucocoricoid recepto is less tolerant).*

This DNA-binding part of the protein actualy consists of two subunits, formed by two proteins. Hence, it is a homo-dimer that binds to the recognition sequence of the DNA which consists of two half-sites each six base pairs long. In case of two identical sets of base pairs the sequence is calleda a response element with *direct repeat*. In cases with a second half-sites containing inverted base pairs, that is the two complementary bases are swapped , this is called an *inverted repeat*. Because of the double-helical architecture of the DNA molecule the “inverted repeat” is the one that has the same bases pointing towards the protein in both half-sites (see. Fig 1).

Experimental data shows that the DNA binding domain of the androgen receptor (AR) and of the glucocorticoid receptor (GR) bind to the same DNA sequence [1]. However, the glucocorticoid receptor has only been observed to bind to inverted repeats whereas the androgen receptor has even been cristallised bound to a direct repeat [1–3]. The DNA binding domains of the two proteins are very similar and differ only by a small number of amino acids.

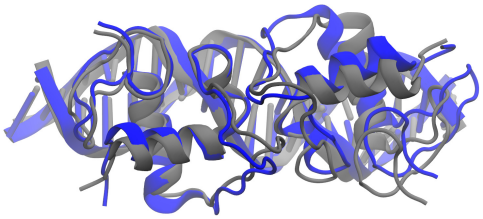


***Abbildung 2:** Binding of the AR protein to inverted (blue) and direct (gey) repeat sequence of DNA.*

Our simulations show that one subunit of AR is slighly rotated upon binding (see Fig. 2) to the less-optimal sequence at the expense of opimal subunit-subunit orientation. The different composition of the corresponding dimer interface compared to the GR likely accounts for sufficiently strong interactions toleaing small such dsiplacements.

It has been shown experimentally that flanking nucleotides modulate GR activity [4]. Moreoever, changing the flanking nucleotides appears to result in a different relative positioning of the dimer-halves (see Fig.3) as shown by our molecular dynamics simulations of complexes of the GR protein to DNA with different flanking bases. Hence, the flanking nucleotides change the three-dimensional structure of the DNA-binding site, the DNA-binding domain of GR and consequently the quaternary structure of the dimeric complex [4].

Further analysis, moreover, shows different flexibility of some parts of the protein, depending on the flanking bases. The highest flexibility is observed for residues at the dimer interface and the connected lever arm. The importance of the dimer interface is further emphasised by mutation experiments that are believed to weaken the interface. In these mutants, the impact of the flanking bases is largely diminished. NMR Spectroscopic data reveals, moreover different, more restricted, conformational dynamics of some residues upon mutation. Prior studies [5] have shown that an intact dimer interface is required to read DNA shape and to direct sequence-specific GR activity. Whether the protein binding and likely also orientation on the DNA is not affected by the flanking bases or this displacement is not recognised through the mutated dimer interface will be shown by further studies.

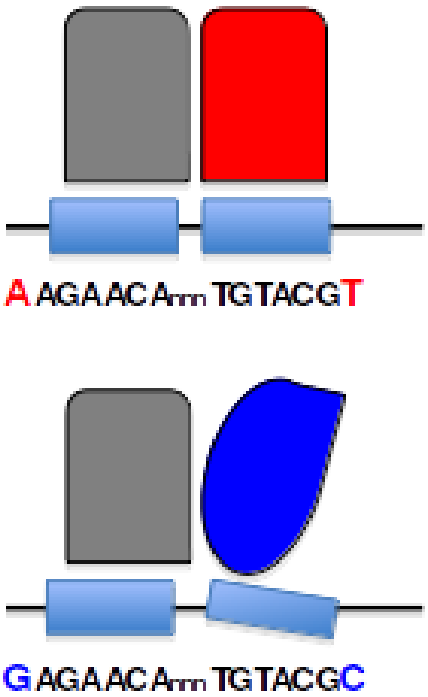


Abbildung 3: *Depending on the flanking (outer) DNA bases, one subunit of the GR protein is more flexible and reoriens on the DNA.*

WWW

http://www.physik.fu-berlin.de

Weitere Informationen

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[3] Sebastiaan H. Meijsing, Miles A. Pufall, Alex Y. So, Darren L. Bates, Lin Chen, Keith R. Yamamoto, DNA Binding Site Sequence Directs Glucocorticoid Receptor Structure and Activity, Science 324, 407–410, (2009).

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[5] L. C. Watson, K. M. Kuchenbecker, B. J. Schiller, J. D. Gross, M. A. Pufall and K. R. Yamamoto, The glucocorticoid receptor dimer interface allosterically transmits sequence-specific DNA signals. Nat. Struct. Mol. Biol. 20, 876â883 (2013).

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