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Leiden  
The Netherlands

## The BRCT domain from the large subunit of human Replication Factor C

Kobayashi, Masakazu

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## STELLINGEN

Behorende bij het proefschrift:

The BRCT domain from the large subunit of human Replication factor C:  
Protein-DNA complex determined by NMR and mutagenesis.

- 1) The N-terminal region of the large subunit of RFC bears two distinct DNA binding activities, 1) 5'-phosphate specific termini binding and 2) non-sequence specific dsDNA binding (Chapter 2 of this thesis and Allen *et al.*, 1996, *Nucleic Acids Res.* 26, 3877).
- 2) Although there is no apparent sequence conservation, the amino acid residues N-terminal to the BRCT domain are essential for dsDNA binding by the large subunit of RFC (Chapter 2 and Chapter 3 of this thesis).
- 3) The BRCT region of the large subunit of RFC does not form a ternary complex with bZIP domain of C/EBP- $\alpha$  while bound to its cognate DNA sequence (Chapter 2 of this thesis) which had been reported previously (Hong *et al.*, 2001 *J. Bio. Chem.* 276, 28098),
- 4) Despite the poor sequence conservation among BRCTs, the residues involved in binding to the phosphate moiety appear to be conserved in the both peptide- and DNA-binding BRCT domains (Willams *et al.*, 2004 *Nat. Struct. Mol. Biol.* 11, 519 & Chapter 3 of this thesis).
- 5) In the proposed model of the protein-DNA complex, the BRCT domain of the RFC presents a shallow, positively charged pocket accommodating the 5' phosphate while additional interactions with the DNA are achieved by the N-terminal  $\alpha 1$  helix (Chapter 5 of this thesis).
- 6) The *in vivo* function of the p140 N-terminal half remains speculative. Although the DNA binding activity of this region may not be essential for RFC function in replication, it might direct RFC to sites involved in other DNA transactions, such as DNA repair or recombination (Uhlmann *et al.*, 1997 *J. Biol. Chem.* 272, 10058).
- 7) The BRCT domain is a phospho-protein binding motif (Manke *et al.*, 2003, *Science.* 302, 636 & Yu *et al.*, 2003, *Science.* 302, 639).
- 8) Several BRCT proteins have now been tested for phospho-peptide binding, although the results found so far are controversial (Willams *et al.*, 2004 *Nat. Struct. Mol. Biol.* 11, 519)
- 9) The remarkable flexibility of the protein-DNA interface of the lac headpiece may primarily originate from the recognition-helix residues sampling different base pair environments in the non-specific complex (Kalodimos *et al.*, 2004 *Science.* 305, 3860).

- 10) “From a drop of water”, said the writer, “a logician could infer the possibility of an Atlantic or a Niagara without having seen or heard of one or the other. So all life is a great chain, the nature of which is known where we are shown a single link of it.” Sir Arthur Conan Doyle
- 11) The strength of the academic research environment is that one is able to exchange ideas and knowledge with each other freely.
- 12) Scientists find some comfort in the Taoist principle “Through working in harmony with life’s circumstances, Taoist understanding changes what others may perceive as negative into positive (a quote from Tao of Pooh by Benjamin Hoff)”