Structural Analysis of the dsDNA- v. ssDNA-binding Protein Interface

Background
Shape and base readout have been shown to be important determinants of double-stranded DNA (dsDNA) binding and specificity. The goal of this project is to examine the readout mechanisms of single-stranded DNA (ssDNA) binding proteins and how these interactions confer recognition, especially in comparison to dsDNA recognition.

Hypothesis
The structural and biochemical properties of a DNA-binding protein allow for specific base and shape readouts that differentiate between ssDNA and dsDNA binding.

Shape Complementarity
Working hypothesis- The charge and shape properties of dsDNA v. ssDNA are complementary to the charge and shape properties of the protein binding interface.

As shown for dsDNA, ssDNA binding also appears to occur through recognition of specific base and shape readouts. The negative charge, size, and high degree of conformation freedom of ssDNA is reflected in the binding surface of ssDNA-binding proteins.

This week’s focus (along with journal club and an exam) was to look more into that shape of the ssDNA-binding protein interface and how it facilitates recognition of ssDNA. Grasp was used to visualize the contour of the binding interface [Gaussian surface, accessibility (0.0, 4.5, 9.0)].
**Summary/Running Conclusion**

ssDNA recognition uses the same base and shape readout mechanism as dsDNA, however the structure and chemical properties of ssDNA lead to different structural and chemical features of the DNA-binding protein interface that confer binding and specificity. Relevant to this week’s work, ssDNA binding appears to occur in interfaces that form a “pocket/groove” at the DNA binding site whereas dsDNA binding tends to involve the ability to insert residues into the major groove. One question is if this can be quantified and shown to be a significant correlate in determining recognition of ssDNA.
Structural Exploration of DNA Recognition by Methyltransferase

Background
DNA methylation has been recognized to play a key role in the regulation of transcription and gene expression through silencing. Therefore, it is not surprising that DNA methylation has been suggested to play a role in cellular disease and dysfunction such as cancer\(^1\). In mammals, methylation occurs at the cytosine C5 position within CpG dinucleotides by DNMT1\(^2,3\). The structure of an auto-inhibited DNMT1 protein in complex with dsDNA has previously been determined (3PT6) and more recently (Science Feb.10, 1012) the structure of an active DNMT1-dsDNA complex was published showing a more intimate complex with dsDNA (have not released coordinates yet... not cool considering it's been published already)\(^3\). In light of Carolina’s nice journal club talk, I was curious and so I figured I'd check it out.

Hypothesis
Minor groove width plays a key role in the shape readout of DNA-methyltransferase recognition and in defining catalytic specificity.

![Graph](image)

**Positive relationship**
**Inverse relationship**
**Optimal range relationship**

Structure of DNMT1 in Complex with dsDNA (3PT6)
Manuscripts

*Early stages of induction of anterior head ectodermal properties in Xenopus embryos are mediated by transcriptional cofactor *ldb1* Carol Zygar Plautz*, Brett E. Zirkle, Malia J. Deshotel, and Robert M. Grainger

*Conserved structural and mechanistic requirements of gp41 MPER-directed antibody neutralization of HIV-1* Ofek, G.*, Zirkle, B.*, Mckee, K., Yang, Y., Zhi-Yong, Y., Nabel G.J., Dimitrov, D., Mascola J.R., Kwong, P.K.

Weekly Papers and One Sentence Summary *(red = next week’s papers)*


Need papers for next week

Questions/Goals for Next Week

Would like to look at electrostatic potential v. at specific bases

- Plot similar to Fig. 3 in Nature 2009 paper