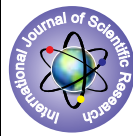


Dna Mimicry by Proteins



Veterinary science

KEYWORDS: DNA, enzyme, protein, mimicry.

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ABSTRACT

Most of the vital body functions are performed by the binding of enzymes to specific regions of DNA, for which it needs to recognize and bind to a target DNA sequence. This is controlled by another protein by direct obstruction of binding site, chemical modification of the binding site, indirect conformational change in the enzyme induced by the binding of the control protein or direct blocking of the DNA binding site on the protein by DNA mimicing. Proteins involved in DNA mimicry is a less explored field. Only a few proteins are reported to have this function which executes its application in a wide range of fields including detection of target DNA binding sites on enzymes and their isolation using the affinity methods. It can target bacterial restriction system, replication, repair and drug resistance, eventually finds its utility in diagnostic and even therapeutic uses of mimic in clinical settings. DNA binding proteins and enzymes are often difficult to crystallize for structural studies. It might be possible to use new DNA mimics, instead of the actual DNA molecule in the preparation of co-crystals aiding in elucidation of the DNA binding site on the target protein. Much more basic research is still to be performed in this area. This mini review details the proteins that function by DNA mimicry and their biological role.

Introduction:

The proteins that can mimic DNA structures can inhibit other proteins that would normally bind to DNA by different ways such as mimicing the phosphate backbone of DNA, the hydrogen bonding properties of the nucleotide bases and bending and twisting of DNA double helix. It covers all known secondary structures of proteins. These mimics tend to resemble distorted DNA rather than the normal one. Side chain carboxylates of glutamates and aspartates can functionally replace phosphates and thereby generate an overall charge pattern resembling DNA phosphate back bone (Dryden *et al.*, 2006). Many proteins like Uracil Glycosylase inhibitor, Ocr, HI 1450, MfpA, dTAFII230, din I and replication protein are reported to have DNA mimicing property. The major proteins involved in DNA mimicry functions and their biological roles are detailed in this article.

1. Ocr (Overcome Classical Restriction):

This protein has amphipathic alpha helices and holds the oldest example of DNA mimicry. It inhibits Type1 DNA restriction and modification mechanism of the host cell. Dimeric Ocr protein encoded by bacteriophage T7 is produced in huge amounts after infection, that overwhelms the host type 1 restriction enzymes. The protein is shown to knock out all sorts of Type 1 restriction endonuclease (RE) enzymes irrespective of their target specificity. Ocr mimics the bent DNA substrate recognized by the Type 1 RE enzyme and the electrostatic mimicry of phosphates by carboxyl groups -1.

2. MfpA (Mycobacterium Fluoroquinolone resistance Protein A):

MfpA protein of *Mycobacterium tuberculosis* binds to DNA gyrase. This protein plays an important role in conferring resistance to fluoroquinolone antibiotics. Fluoroquinolones irreversibly inhibit DNA gyrase, an essential enzyme in bacteria. Quinolone tolerance is now widely emerging clinically and appears to be related with the acquisition of the horizontal *qnr* gene transfer. The recent structure of MfpA, a *qnr* gene product encoded by *Mycobacterium tuberculosis* shows dimeric structure 10nm in length with a diameter of 2nm at dimer interface and surface having enough carboxyl groups. MfpA binds to DNA gyrase and rescues it from the inhibition by the

quinolone drugs. The protein fits well in to a DNA binding site on the target enzyme, there by mimicing theDNA. Binding of MfpA to the gyrase maintains the enzyme in an active form until required, thereby effectively reducing both the binding of quinolones to the gyrase and its clinical efficacy (Dryden *et al.*, 2006).

3. UGI (Uracil Glycosylase Inhibitor):

UGI, an acidic protein (84 amino acids) is encoded by *Bacillus subtilis* phage (PBS2). Uracil in DNA arises from the occasional incorporation of dUTP during replication or spontaneous deamination. UDGs remove the uracil bases from the DNA by the base excision repair pathway. Some DNA viruses such as, herpes virus and pox virus also encode UDG activity and it appears to have an important role in virus replication. UDGs are emerging as attractive therapeutic targets due to their role in wide range of biological processes. Hence, the discovery of small molecules which are able to inhibit the particular UDGs has acquired a great interest. The first natural UDG inhibitor reported was UGI. The X-ray crystal structure of UGI in complex with different UDG's revealed that UGI's mimics the electronegativity and structural features of duplex DNA. UGI mimic only a very short section of DNA (Acharya *et al.*, 2002; Sudip *et al.*, 2000).

4. p56:

This is reported to be a novel inhibitor of the *Bacillus subtilis* uracil glycosylase. p56 is an acidic protein (56 amino acids) encoded by the *Bacillus subtilis* lytic phage 29. The protein p56 is synthesized upon phage 29 infection and knocks out a host encoded base excision repair system. The results revealed that the protein p56 blocked the DNA binding site of UDG (Heras *et al.*, 2007).

5. RP-A (Replication Protein A):

Human replication protein A (RP-A), also known as human single stranded binding protein, is a multi subunit complex involved both in replication and repair. It is capable of forming complex with tumor suppressor protein p53. p53 is unable to prevent RP-A from associating with a range of ss DNA. RP-A is able to inhibit p53 strongly from functioning as a sequence specific DNA binding protein when the two protein are com-

plexed. Increasing p53 concentration can overcome the inhibition by steady state levels of RP-A. It has been studied that p53 can itself be stimulated for specific DNA binding when complexed through the C terminus with short single strands of DNA. These results identify a potential dual role for single stranded DNA in the regulation of DNA binding by p53 and gives possible insights in to the p53 response to DNA damage (Miller *et al.*, 1997).

6. dTAF1 (*Drosophila* TAF1):

dTAF1, previously known as dTAF₁₁, 230 is a protein derived from *Drosophila* that acts as a regulator of TBP (TATA Box binding protein). It is an example of sequence specific DNA mimicry. The protein can mimic the structure recognized by TBP. TBP interacts with the phosphates using two rows of lysine and arginine and two asparagine residues which are in the middle of binding surface. These residues would then hydrogen bonds with the DNA bases and four phenylalanine residues partially force their way in to the DNA in order to create a major distortion of DNA. The TBP core has a highly symmetric structure resembling a molecular 'saddle'. The concave face of the saddle plays an important role in TATA box binding, whereas the convex face provides interaction sites for several initiation factors that include TFIIA, TFIIB, and dTAFII42. dTAF1 has two rows of acidic amino acids to interact with the arginine and lysine residues; a methionine residue and several main chain peptides hydrogen bonds to two asparagine. Two large concave hydrophobic surfaces interact with phenylalanine. Therefore, dTAF1 is a very precise mimic of the grossly distorted DNA structure bound by TBP (Putnam *et al.*, 2005).

7. DinI (Dark Inducible):

DinI protein of *E. coli* is a down regulator of SOS response that appears to interfere with RecA-DNA filament. The structure reveals the presence of a single amphipathic alpha helix exposing acid residues along one face of the helix. The helix can mimic the single stranded DNA substrate recognized and bound by RecA. DinI is a mimic of the phosphate backbone of single stranded DNA.

Conclusion

From the discussion, it could be envisaged that DNA mimics could be used in the following increasingly speculative areas like detection of target DNA binding sites on enzymes and their isolation using the affinity methods. It can target bacterial restriction system, replication, repair and drug resistance, thus diagnostic and even therapeutic uses of mimic in clinical settings might eventually possible. DNA binding proteins and enzymes are often difficult to crystallize for structural studies. It might be possible to use new DNA mimics instead of actual DNA molecule in the preparation of co-crystals to aid elucidation of the DNA binding site on the target protein.

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