



RRST-Biochemistry

# Immunoglobulins may Modulate the Formation of Triple Helix DNA in Pathophysiological States

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Article Info	Abstract
<p><b>Article History</b></p> <p>Received : 13-03-2011            Revises : 30-03-2011            Accepted : 01-04-2011</p> <p><b>*Corresponding Author</b></p> <p>Tel : +91-416-228-4237            Fax : +91-416-228-4237</p> <p>Email:  <a href="mailto:tyagi257@yahoo.in">tyagi257@yahoo.in</a></p> <p>©ScholarJournals, SSR-SILAE</p>	<p>The Runt domain proteins are comprised mostly of <math>\beta</math>-strands arranged in an antiparallel fashion to form a <math>\beta</math> barrel with an s-type immunoglobulin fold. It is interesting to note that the same fold is used in the DNA binding domains of several transcription factors. A common feature is that DNA binding is mediated by loops that extend from one end of the Ig-motif. These proteins bind to different DNA sequences and specific recognition is accounted for by variations in the details of the molecular interactions between the loop regions and the DNA. This review suggests that immunoglobulin fold proteins may play a key role in modulation and formation of triple helix DNA structure with implications for patho-physiological states.</p> <p><b>Key Words:</b> Immunoglobulin, DNA, Triple helix, Transcription, Loop</p>

## Introduction

Recent structures of the Runx1-CBF $\beta$  heterodimer bound to DNA brings to six the number of characterized eukaryotic transcription factor families that use an immunoglobulin (Ig) fold to bind to DNA [1]. Variation in the loop regions accounts for the diversity of DNA sequences recognized by Ig-fold proteins, but there are recurring themes in the interactions made by specific loop regions and how these interactions are regulated.

It is interesting to note that this same fold is used in the DNA-binding domains of several other important transcription factors in animals, including NFAT [2], NF- $\kappa$ B [3], p53 [4], STAT [5] and the Brachyury T-box [6] family of proteins [7]. A common feature is that DNA binding is mediated by loops that extend from one end of the Ig-motif (Figure-1). These proteins bind to different DNA sequences and specific recognition is

accounted for by variations in the details of the molecular interactions between the loop regions and the DNA. An excellent example of the way the conformation of this C-terminal tail (and therefore DNA binding) can be regulated by protein-protein interactions is provided by the structure of the STAT proteins. The STAT proteins bind DNA as dimers that form in response to phosphorylation of an SH2 domain that is C-terminal to the Ig-fold DNA-binding domain. The C-terminal tail of the STAT Ig-fold makes many contacts to DNA and is inserted deeply into the major groove. The position of this tail segment is stabilized by packing against a helix from the linker region between the Ig-motif and the SH2 domain. Thus immunoglobulins *per se* and their Ig fold containing proteins may play an important role in novel DNA binding.

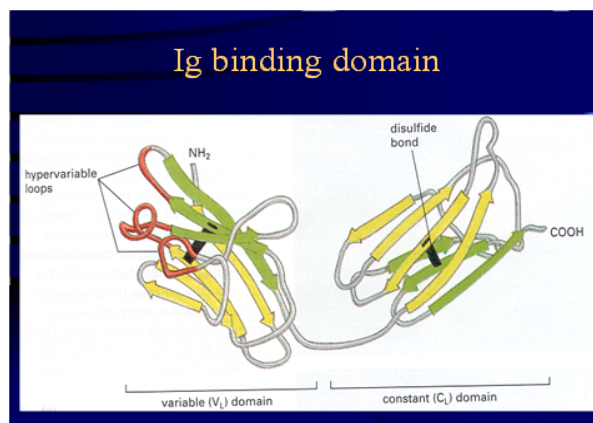


Figure 1

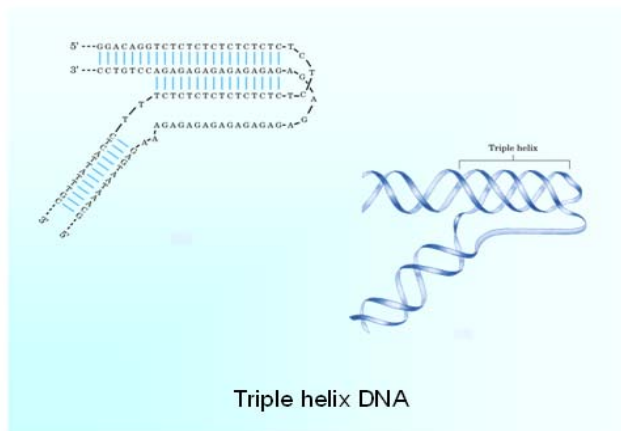


Figure 2

### Triple helix or Non-B DNA

On the other hand, triple helix formation recently has been the focus of considerable interest because of possible application in developing new molecular biology tools as well as therapeutic agents [8] and because of the possible relevance of H-DNA structures in biological systems [9]. In intermolecular structures, an oligopyrimidine-oligopurine sequence of DNA duplex is bound by a third-strand oligonucleotide in the major groove [10]. Two main types of triple helices have been described, depending on the orientation of the third strand [11]. The first reported triple-helical complexes involved pyrimidic third strand whose binding rests on Hoogsteen hydrogen bonds between a T-A base pair and thymine, and between a C-G base pair and protonated cytosine [12,13] (Figure 2). Triple helix DNA can also be used in gene therapy where they target DNA sequence of mutated gene to prevent its transcription. Purine-rich tracts are frequently found in gene promoter regions and triple helix forming oligonucleotides directed to these regulatory sites have been shown to selectively reduce transcription of the targeted genes, likely by blocking binding of transcriptional activators and/or formation of initiation complexes.

### Immunoglobulin binding to DNA

A s-type immunoglobulin (Ig) fold has been shown by NMR spectroscopy in the DNA binding domains of NFAT, p53, NF-Kappa B, STAT-1 and the T-domain. The structural and functional similarity among these proteins indicates that the DNA binding domains of these proteins form a family of structurally and functionally related proteins. The determinants for DNA binding on the Runt domain have been mapped from a combination of intermolecular structures showing that DNA binding is mediated via the loop regions of the Ig fold, as is seen for the other members of this family. Thus the Ig motif has several loops and these proteins bind to different DNA sequences and specific recognition is accounted for by variations in the details of the molecular interactions between the loop regions and the DNA. These loops are designated as A-B loop, E-F loop, C-D loop, and the C-terminal tail. Studies conducted by Mol *et al* [14] showed that triple stranded DNA has a complementarity determining region where the antibody make a specific contact with the DNA bases in the minor

groove of the triplex. Alternate DNA structures other than double-stranded B-form DNA can potentially impede cellular processes such as transcription and replication. In the similar way these Ig loops can modulate the binding to the DNA triplex helix and G4 tetraplex structures that form by Hoogsteen hydrogen bonding are two examples of alternate DNA structures that can be a source of genomic instability. Thus it is speculated that the Ig has the ability to alter human replication protein A (RPA), a single-stranded DNA binding protein that is implicated in all facets of DNA metabolism, to destabilize DNA triplexes and tetraplexes.

### Implication of Ig binding and triple helix formation for disease states

Ig binding domain may mediate the interaction with triple helix DNA and may modulate the formation of triple helix DNA and may have potential role in pathophysiological states. Triplet repeat tracts have been shown to form non-B DNA structures. Many hereditary neurological diseases are caused by the expansion of triplet repeat sequences in either coding or noncoding regions [15]. Such triplet expansion is mediated by DNA replication, recombination or repair, and the precise mechanisms are still under investigation. DNA slipped structures and preferential formation of DNA hairpin structures, in addition to triplexes or tetraplexes appear to be important reasons for the genetic instability in these cases.

### Conclusion

It is presumed that interactions with other DNA-bound transcription factors are responsible for determining whether the output is activation or repression. It seems likely that the Runx-CBF  $\beta$  module will provide a novel molecular apparatus for sensing the presence of other DNA-bound factors and translating these interactions into coherent signals for transcriptional regulation. The structure of the Runx1-CBF  $\beta$ -DNA complex [16] provides an essential starting point for delving further into the mysterious and unexplained properties of this interesting and important family of DNA-binding, developmental regulators. A common feature is that DNA binding is mediated by loops that extend from one end of the Ig-motif. These Ig motif containing proteins bind to different DNA sequences and specific recognition is accounted for by variations in the details of the molecular interactions between

the loop regions and the DNA and thus may therefore modulate the formation of triple helix DNA in various pathophysiological states.

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