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Minor groove interactions of AT-rich DNA with dicationic drugs and proteins.

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AT-rich DNA is mainly found in non-coding regions in eukaryotes, it represents a large portion of genomes. It is known that some of these non-coding regions play an important role in regulation, transcription and signaling. Some proteins interact with AT-rich DNA as architectural proteins that affect cellular functions by modulating chromatin structure. Moreover DNA of several pathogens is very rich in AT base pairs. Typical examples include the malaria parasite *Plasmodium falciparum* which has 80% AT-DNA and is the causative agent of malaria.

This fact has prompted studies of drugs which interact with the minor groove of DNA. We present the crystal structure of the complex of the DNA duplex d(AAAATTTT)₂ with the dicationic drug 4,4'-bis(imidazolinylamino) diphenylamine (CD27), an antiprotozoal drug. It completely fills the minor groove of DNA preventing the access of proteins and displaces bound water. The drug protrudes from the DNA and interacts with neighboring molecules, so that it may act as a cross-linking agent. These findings allow a better understanding of this family of compounds and will help in the development of new, more effective drugs.

This type of agents may prevent the access of proteins such as high mobility group (HMG) proteins to DNA. We have studied the interaction of HMGA and HMGB proteins with AT-rich DNA. We have found a novel mode of DNA recognition of box-A from HMGB protein, it reveals a mechanism by which structure-specific HMG boxes kink and underwind linear DNA.

References

Web page of MACROM group

Acta Cryst (2014), D70 pp.1614-1621 F.J. Acosta-Reyes et al. (PDB: 4OCD)

Acta Cryst (2015), D, (in press). R. Sánchez-Giraldo et al.

Caption (s) - Add figures as attached files (2 fig. max)

Fig. 1.- Complex of drug CD27 with AT-rich DNA. Fig. 2.- Protein HMGB boxA with AT-rich DNA

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