Chemistry & Biology, Vol. 9, 399–401, April, 2002, PII S1074-5521(02)00128-X

Preview

Damage Control of DNA in Nucleosome Core Particles: When a Histone's Loving, Protective Embrace Is Just Not Good Enough

Packaging DNA into nucleosome core particles generally offers protection from damage by molecules diffusing in solution. However, on page 403 of this issue, Barton and coworkers report that although noncovalently bound, activated Rh (Rhodium) does not readily bind within nucleosomal DNA, activated Rh that is covalently tethered to the 5′ terminus of a histone-associated oligonucleotide oxidizes guanine bases from a distance of up to 24 base pairs, demonstrating that histones do not protect DNA from long-range damage from the transport of charge through stacked bases. This implies that oxidative damage generated on DNA in vivo may spread from an initially damaged site to distal sites. Once created, such sites may persist and be resistant to repair because of the protective packaging by histones; they thus may result in permanent mutations.

An obvious feature of the classical model of the DNA double helix is the strong π-orbital overlap that inspires images of the possible role of the DNA double helix as a "π-way" for charge transport [1]. The issues surrounding charge transfer have attracted the attention of chemists and biochemists for decades [2]. One issue is the ability of the double helix to serve as a "passive" wire to conduct charge from a donor site to an acceptor site. A second issue is the ability of the double helix to serve as a reactant during the charge transfer process. Typically, the 5′ guanine of 5′-GG3′ sites are selectively oxidized. Strikingly, the oxidized guanines can be located at a considerable distance, over many bases, from an initial site of charge creation.

Given the strong interest in the charge transfer process and the possible role of the double helix in "synthetic" systems, it is natural to investigate the possible relevance of charge transfer in biologically relevant systems. In particular, the DNA in cells is typically "packaged" by a variety of proteins that serve to regulate replication, transcription, and repair. The investigation reported by the Barton group in this issue examines a DNA packaged in a histone octamer and a 146 base pair palindromic DNA sequence. Both the histone and DNA are well characterized structurally. In each half of the palindrome, the DNA possesses seven 5′-GG-3′ sequences (termed GG1, GG2, GG3, etc), which are expected to be the most easily oxidized sites along the double helix. The double helix was oxidized by direct photochemical excitation, by photochemical excitation of a noncovalent Rh(III) metal complex, and by photochemical excitation of a Rh complex covalently tethered to the 5′ terminus of the double helix. The results indicate that even the relatively "inaccessible" histone-packaged DNA is unprotected from oxidation by the photochemically excited noncovalent Rh complex and that oxidation occurs not only at the GG sites but also randomly over the DNA double helix.

The salient result of the research is that the histone-packaged DNA possessing the Rh complex covalently bound to the 5′ terminus of the double helix is nearly the same in the presence or absence of histones. This observation is consistent with an identical intercalation of the Rh complex into the double helix and an identical charge transport for both the histone-packaged DNA and the "unpackaged" DNA. It is striking that, despite the large number of factors that could have potentially led to a difference between the two systems, the pattern of oxidation of the guanine is relatively unchanged by DNA packaging by histones. An interesting feature of this system is that oxidation is observed for the GG1, GG2, GG3, and GG4 sites but not for the GG5, GG6, and GG7 sites. This result indicates that the range of transportation of oxidative charge through DNA is limited; however, the effects of charge transport and damage were detectable for a distance of 24 nucleotide base pairs from the initial source of oxidation.

These results have implications for the damage and repair of DNA that is bound to nucleosome core particles. For example, nucleosomes are considered to "package" DNA in cells, and the notion of packaging implies protection. However, this report demonstrates that electron transfer processes that employ the base pair stack as a path for long-range charge transfer that damages can override the nucelosome's protective function and embrace.

Nicholas J. Turro
Department of Chemistry
Columbia University
3000 Broadway, MC 3119
New York, NY 10027

Selected Reading

1. Purugganan, M.D., Kumar, C.V., Turro, N.J., and Barton, J.K. (1988). Accelerated science electron transfer between metal complexes mediated by DNA. Science *241*, 1645–1650.
2. Schuster, G.B. (2000). Long-range charge transfer in DNA: transient structural distortions control the distance dependence. Acc. Chem. Res. *33*, 253–260.
3. Lewis, F.D., and Letsinger, R.L., and Wasielewski, M.R. (2001). Dynamics of photoinduced charge transfer and hole transport in synthetic DNA hairpins. Acc. Chem. Res. *34*, 159–170.
4. Giese, B. (2000). Long-distance charge transport in DNA: the hopping mechanism. Acc. Chem. Res. *33*, 631–636.
5. N.J. Turro and J.K. Barton (1998). Paradigms, supermolecules, electron transfer and chemistry at a distance. What's the problem? The science or the paradigm? J. Bio. Inorg. Chem., 201–209.