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Electron transfer through DNA and peptides

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Abstract—Electrons can migrate through DNA and peptides over very long distances in a multistep hopping process. Stepping stones, which carry the charges for a short time, are the nucleotide bases of DNA or the aromatic side chains of amino acids in peptides. Chemical reactions of these charged intermediates lead to the formation but also to the repair of DNA lesions. In enzymes, long distance electron transfer can activate the binding pocket, and initiates the chemical transformation of the substrate.

1. Introduction

In the last decade it became evident that electrons and electron holes migrate through DNA over long distances.[1–6] Thus, if a guanine base of a DNA-nucleotide is ionized under oxidative conditions, the electron hole can migrate through the DNA double strand before reaction with water and oxygen occurs yielding reaction products like the mutagenic 8-oxoguanine. As a consequence, the site of oxidative attack at the DNA and the site of DNA lesion can be far away from each other (Fig. 1). This long distance electron hole transfer might protect the coding area of DNA against oxidative stress.[7] Upstream of many coding areas are guanine-rich sequences, which are thermodynamic sinks for the positive charge. This driving force induces hole migration from a coding area to the uncoding area and produces a lesion in the uncoding area even if the oxidative attack has taken place at a base in the coding area.[7]

Excess electrons also travel through DNA over long distances.[5] Thus, if thymine is reduced to a thymine radical anion, the electron can migrate to a distant DNA site before a chemical process occurs, for example the cleavage of a thymine dimer (Fig. 1).[6] This process repairs UV-induced mutagenic DNA lesions.

2. Mechanism of electron transfer through DNA

How is it possible that charges can migrate over long distances through DNA before the radical ions of the nucleotide bases are trapped in chemical reactions? In order to answer this question, we have developed methods for site-selective injection of a positive charge into guanine[3] and site-selective injection of a negative charge into thymine.[8] Guanosides[9] and thyminidines[8] were synthesized that carry ketone groups as radical precursors. Photolysis yielded radicals that cleaved heterolytically their β-bonds forming alkyl radical cations,[10] and anions[8] respectively, which generated radical ions of the directly bound bases (Fig. 2).[8,11]

The efficiency of the charge transfer through DNA was measured by chemical trapping of the nucleotide base radical ions (Fig. 1). In 1998, we observed that long distance hole transfer through DNA oligomers occurs in a multistep hopping mechanism, where the guanines are the stepping stones, which temporarily carry the positive charge.[12] The intervening adenine bases are not oxidized but they mediate the orbital interactions between the guanine radical cation (electron hole donor) and the guanine (electron hole acceptor).[13] This is now called the G-hopping mechanism. However, three years later it became obvious that in oligonucleotide sequences, where the guanines are separated from each other by more than three adenine bases, also the adenines are charge carriers.[14] Obviously, the endothermic oxidation of an adjacent adenine by the guanine radical cation is faster than the thermoneutral oxidation of a distant guanine. Once an adenine is oxidized to an adenine radical cation the hole transport over long adenine:thymine

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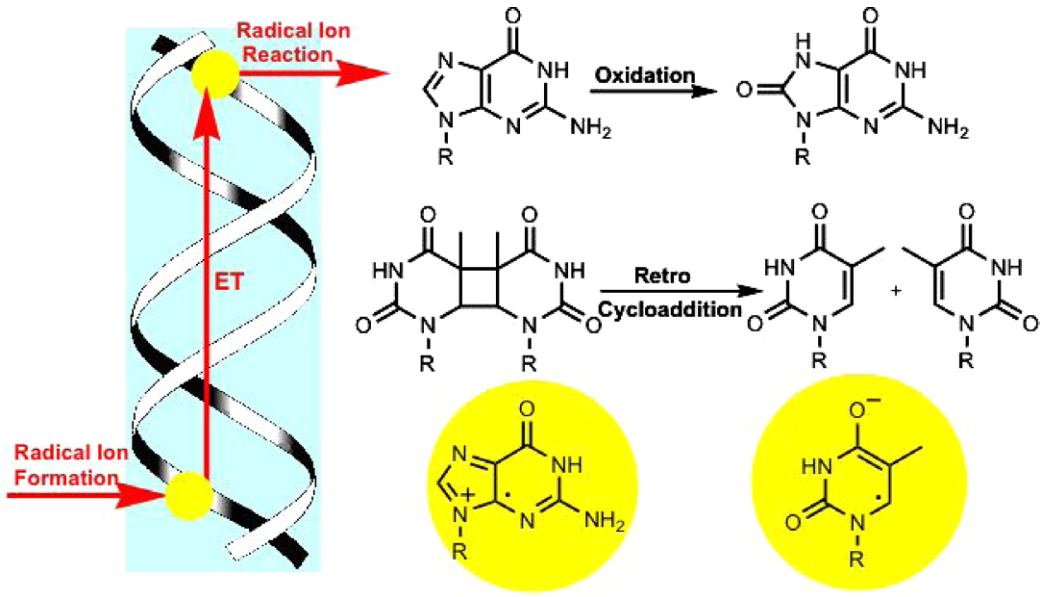

Figure 1. Electron and electron hole transfer through DNA, which leads to chemistry at a distance.

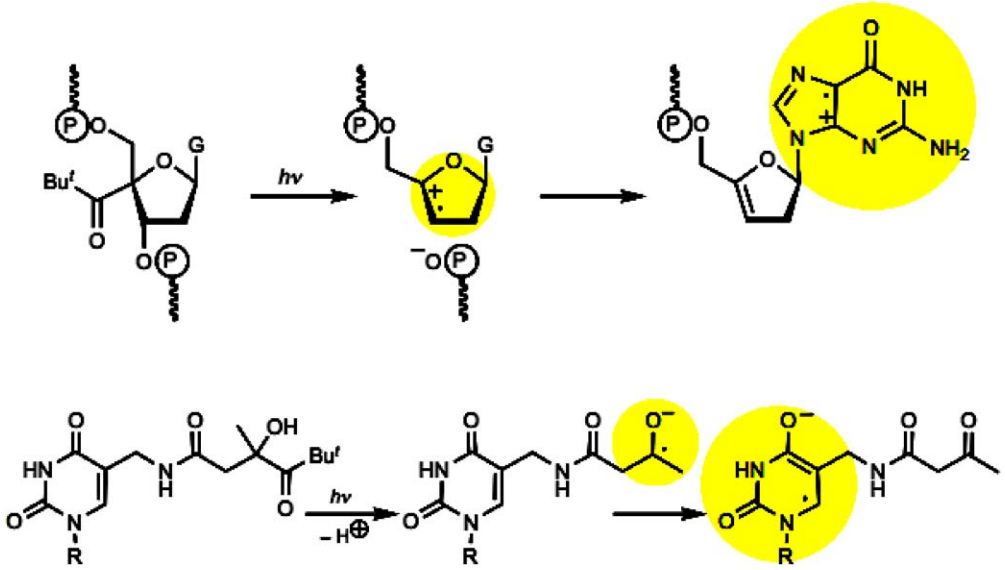

Figure 2. Generation of guanine radical cation and thymine radical anion.

sequences in a hopping mechanism is very efficient (A-hopping).

Excess electrons also migrate in a multistep hopping process through DNA. However, stepping stones for the electrons are the pyrimidine bases of DNA. Because the difference of the redox potentials between thymine and cytosine is smaller than that between guanine and adenine, the DNA sequence has a weaker influence on the excess electron transfer than on the hole transfer. We determined the migration of electrons through DNA by cleavage of thymine dimers (Fig. 3).[8] During this chemical reaction the charge is not destroyed, therefore one electron can cleave several thymine dimers. The electron catalyzes the repair of the DNA photolesion.[8]

3. Mechanism of electron transfer through peptides

Long distance charge transfer is not restricted to DNA, where the heterocycles are donor and acceptor groups, also proteins are efficient biopolymers for charge transport. In the enzyme ribonucleotide reductase, as an example, a tyrosine radical is generated 3.5 nm away from the site where ribonucleotide is reduced to deoxyribonucleotide. The electron hole has to travel this distance in order to generate a thiyl radical that catalyzes the deoxygenation reaction (Fig. 4).[15]

It is highly likely that aromatic and heterocyclic side chains of amino acids are the charge carriers, and charge transfer again occurs in a hopping mechanism. In order to test, whether electrons can migrate not only through

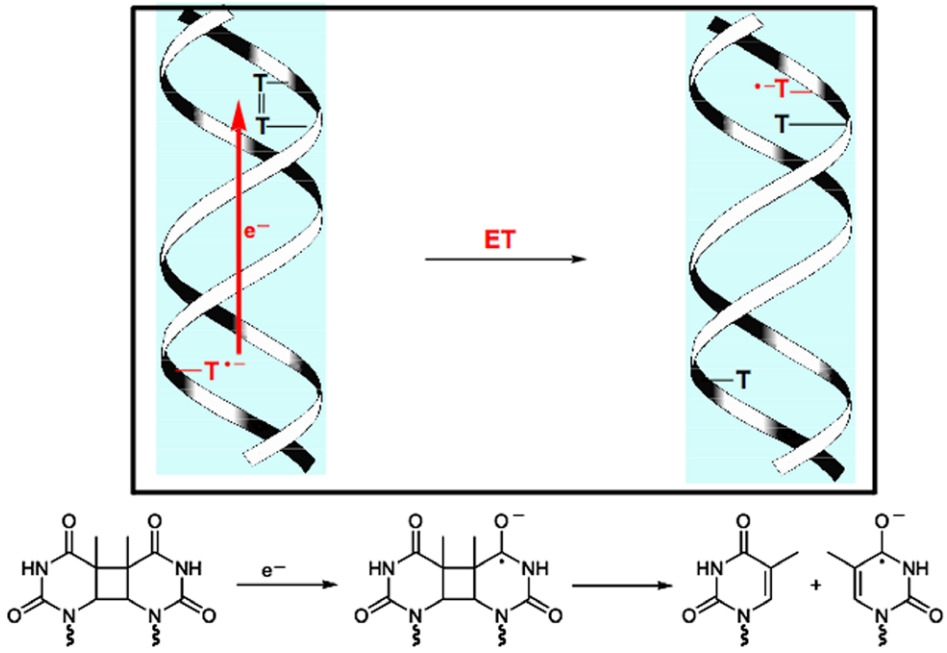

Figure 3. Cleavage of a thymine dimer induced by long distance electron transfer from a thymine radical anion.

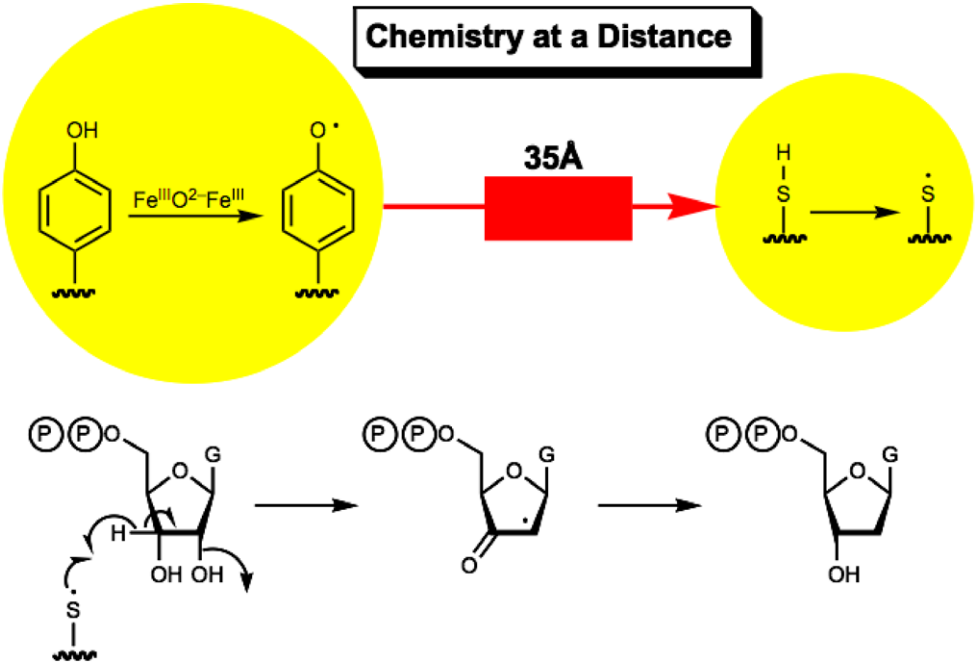

Figure 4. Electron transfer and chemical reduction of the substrate by the enzyme ribonucleotide reductase.

peptide bonds but also through space we have started to study this process.[16] In our model systems tyrosine and trimethoxyphenyl alanine are used as amino acids, which are separated from each other by proline spacers (Fig. 5).

Similar to the DNA assay, oxidation of peptides was triggered by a ketone containing injection system. Photolysis generated an enolether radical cation, which oxidized the aromatic side chains. In the example of Figure 5 the charge was transferred to trimethyoxyphenyl alanine, the nearest amino acid, and migrated to tyrosine in the next step. The radical cation of trimethoxyphenyl alanine has a UV maximum at 550 nm and the tyrosyl radical, generated from the tyrosine radical cation by rapid deprotonation, absorbs at 410 nm. The spectra in Figure 5 demonstrate that 15 ns after the laser pulse only the radical cation of the trimethoxyphenyl alanine was formed, but in the next step the charge hops to the tyrosine. We measured the reaction rates of this intramolecular hopping process and observed that the number of prolines between these amino acids decreased

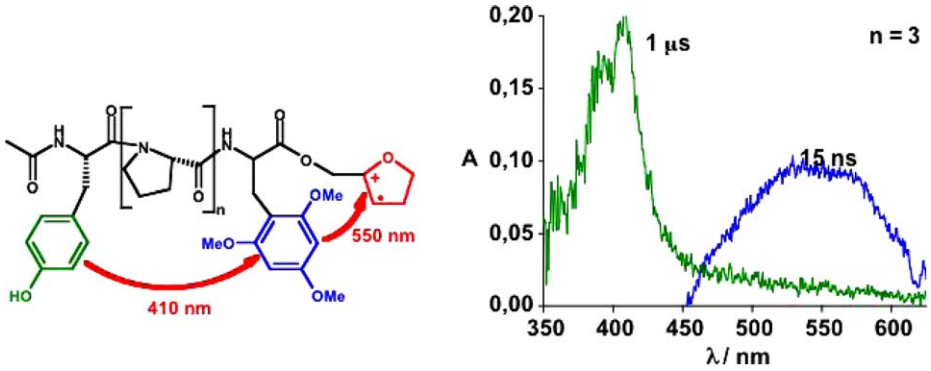

Figure 5. Electron hopping in a model peptide. The spectrum shows the appearance of the oxidized side chains at different times.

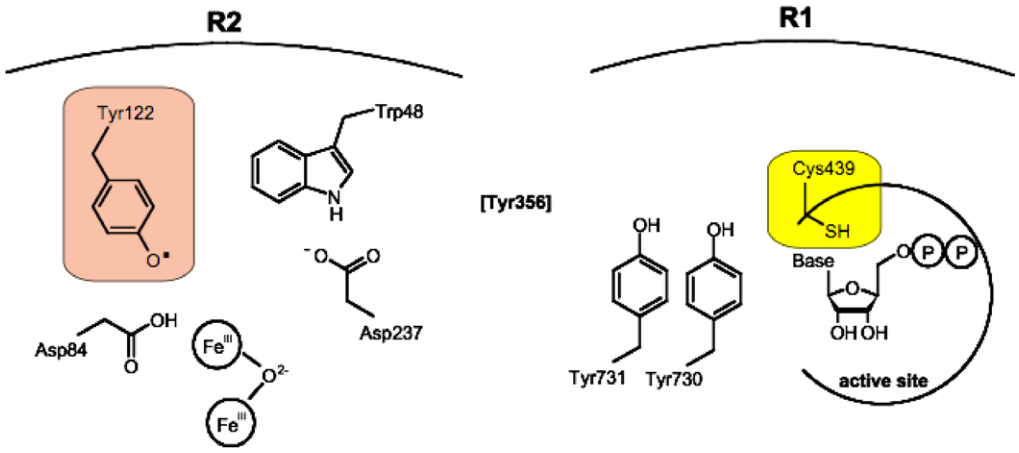

Figure 6. Possible amino acids involved in the long distance electron transfer from Tyr122 to Cys439.

the rate only slightly.[16] This is not compatible with an electron transfer through the peptide bonds, for which a strong rate decrease is expected if the spacer is increased by two proline molecules.[17] We therefore concluded that the electron hole directly hops between the aromatic side chains using the solvent as mediator.

Thus, long distance charge transport through biopolymers occurs in a multistep hopping mechanism. But the distance dependence of the individual hopping steps is smaller in DNA than in peptides because the DNA bases are more efficient as mediators of the charge transport than the solvent in peptides. However, peptides are more flexible than DNA double strands, and the distances between side chains of amino acids in peptides can often be reduced by conformational changes. This flexibility facilitates long distance charge transfer in the enzyme ribonucleotide reductase (Fig. 6).

The long distance between tryptophan at position 48 in the subunit R1 and tyrosine at position 731 in the subunit R2 is bridged by tyrosine at position 356. Because X-ray studies have shown that this amino acid is very flexible, one can assume that the charge is transported between the subunits R2 and R1 using this tyrosine as a mobile charge carrier.[15]

4. Conclusion

Long distance electron transport through the biopolymers DNA and proteins occurs in a multistep hopping reaction. The heterocyclic bases of DNA and the aromatic side chains of amino acids in peptides act as charge carriers. These long distance electron transfer processes play important roles in biological reactions.

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