Charge transfer in DNA and repair of oxidative damage

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Abstract. The possibility of a biological role of an unusual function of DNA sequences is discussed, namely, signaling by charge transfer within chromatin. Although a general conclusion on its biological significance is premature, the idea of charge transfer accompanying repair of some types of oxidative DNA damage is based on sound experimental data. Both physical and chemical experiments reviewed here provided results indicating that DNA duplex under certain conditions (among them – hydration) – can behave as narrow band gap semiconductor. With the use of model molecules it was shown that charge transfer most probably occurs by hopping between guanine residues and tunneling through thymine-adenine (TA) base pairs. Charge transfer is nucleotide sequence and distance dependent. Furthermore, the π-stacked base pairs must be perfectly matched to mediate charge transfer and in a damaged double helix this condition is not fulfilled. Hence, the possibility that charge transfer takes place in oxidatively damaged DNA after UV or X-irradiation and it becomes interrupted by mismatched base pairs, thus signaling the mismatch or strand break to the repair machinery. Function of base damage repair enzymes which contain [4Fe-4S] clusters is discussed in this context.

Key words: charge transfer in DNA • DNA repair • oxidative base damage • base damage excision • 4Fe-4S cluster • MutY glycosylase • photolyase

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Introduction

The genome usually is regarded as a collection of genes, coding specific DNA types, either regulatory or spliced and translated into amino acid sequences, thus producing about 30000 proteins in an average cell. The role of the coding DNA sequences is firmly established, whereas that of the non-coding ones is not sufficiently explained. On the one hand, there is a tendency of treating this DNA as junk – an idea much publicized by Dawkins [11]. On the other hand, deletions in these sequences were shown to adversely affect cells. Such is the case of the intron sequences which are transcribed but not translated (e.g. [29]) and conserved non-coding elements (CNEs) that act as cell type specific enhancers of gene transcription [1, 2, 25, 35]. Transcriptional regulatory functions to conserved non-coding sequence elements were assigned in several studies and shown to be important in the embryo development (e.g. [38, 40, 44]. A good part of DNA is a collection of repetitive sequences, tandem short repeats, pseudogenes and transposable elements of varied origin and function. Therefore, the view of intergenic sequences as junk is being little by little abandoned.

In this paper, another function of DNA sequences is discussed, namely, signaling by charge transfer within chromatin. One can ask whether some DNA stretches are specialized in transmission of signaling different from that of protein kinase cascades. Although

a general conclusion of this kind is premature, charge transfer accompanying repair of some types of oxidative DNA damage is based on sound experimental data, as reviewed below.

Charge transfer in DNA – sequence and distance dependence

The unusual structure of the DNA double helix with the complementary match of base pairs explains its replication and transcription ability. The structural features also are favorable for charge transfer. The perfectly matched base pair stack is one pre-requirement for efficient charge transfer, whereas nucleosomal structure is not an impediment [31, 32]. On the other hand, some proteins, when complexed to DNA, can modify the extent of charge transfer (see below).

Various experimental approaches were used to study charge transfer in DNA. The physicists measured the current flow in DNA fibers [13] or in aligned DNA films [33]. It should be stressed that the electron conductivity was found mostly in dry DNA, a situation not comparable with that *in vivo*. Moreover, a recent work [5] indicated that in hydrated DNA "…hydrogen links of the nucleobases with water molecules lead to a shift of the pi electron density from carbon atoms to nitrogen atoms and can change the symmetry of the wave function for some nucleobases. As a result, the orbital energies are shifted which leads to a decrease in the potential barrier for the hole transfer between the G-C and A-T pairs from 0.7 eV for the dehydrated case to 0.123 eV for the hydrated". This statement is of considerable significance for biologists, as the energy barrier seemed to be a major impediment for accepting the possibility of a biological role of charge transfer.

Experiments carried out with chemical or biochemical methods and model molecules gave well founded and consistent results. Most of the work has been carried out at the California Institute of Technology (reviewed in [7, 8, 27]). In experiments with the use of model duplex oligodeoxynucleotides, photooxidants were intercalated or appended to the molecules of defined deoxynucleotide sequences. On photo-excitation, guanine (G) doublets placed at a defined distance from the photooxidant residue became oxidatively damaged and the extent of damage could be determined. This effect has been called long-range oxidative damage [43]. Among the photooxidants used in these experiments were ethidium covalently bound to the DNA stretch [19, 21] and a Rh intercalator, Rh(phi$_2$)(bpy')$^{3+}$, where phi is 9,10-diimine phenanthrenequinone and bpy' is 4'-methyl bipyridine-4-butyric acid [18]. Alternatively, the extent of quenching of the fluorescence of the Ru II (dipyridophenazine complex by the intercalated Rh-complex was measured [3, 30]. A diagram of experiment involving fluorescence quenching and its inhibition by mismatch introduction into the "DNA bridge" is shown in Fig. 1.

By changing the number of base pairs and the deoxynucleotide sequence it was possible to modulate charge transfer and several conclusions could have been drawn:
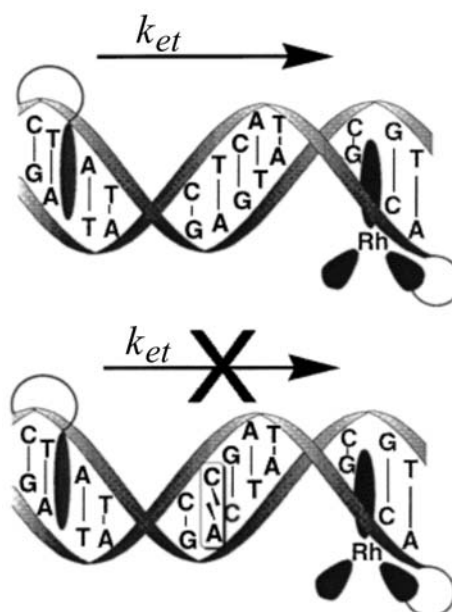

Fig. 1. Fluorescent quenching experiment [37]. A DNA duplex is tethered to an ethidium intercalator that is paired with the rhodium intercalator, Rh(phi)$_2$bpy']$^{3+}$ (see text for explanation). The two intercalators form a system in which ethidium is the photooxidant and Rh complex a quencher of the fluorescence. Reproduced by permision of Elsevier from Rajski SR, Jackson BA, Barton JK (2000) DNA repair: models for damage and mismatch recognition. Mutat Res 447;1:49–72.

– Charge transfer in DNA occurs by hopping between guanine residues and tunneling through thymine-adenine (TA) base pairs [8, 34];
– Charge transfer is sensitive to base pair stacking [21–24, 28] and one mismatch is sufficient to inhibit charge transfer [23];
– Long-range charge transfer is dependent on distance and is modulated by the intervening deoxynucleotide sequence and sequence-dependent dynamics.

The latter point needs some comments. Examination of the effect of distance on charge transfer in the model deoxyribonucleotide duplexes revealed a shallow dependence [30] and, in contrast, a strong dependence on the intervening sequence of deoxyribonucleotides. The presence of 5'-TA-3' repeats causes a substantial decrease in charge transfer. This is in agreement with the prediction that the rate of CT mediated by tunnelling (TA pairs) decreases exponentially with increasing distance, whereas for the hopping mechanism (GC pairs) the distance dependence is shallow [6, 15, 16].

Examination of the effect of temperature between 5 and 35°C on CT has shown an increase in the proportion of long-range CT (> 100 Å) occurring at higher temperatures [30, 34]. This effect is interpreted in [34] as conformationally gated hopping among stacked domains where enhanced DNA base motions at higher temperatures (yet below the DNA melting point) lead to longer range charge transfer.

Charge transfer in DNA complexed with proteins

In contrast to the experiments with model molecules described above, DNA in the nucleus is never "naked". Hence, the importance to understand how proteins

affect charge transfer in DNA. According to the previously stated regularity, any distortion in the double helix will impair charge transfer and this is indeed the case. In experiments by Rajski and Barton [36], DNA constructs were used that contained specific binding sites for the different proteins under examination. A rhodium intercalator tethered to the DNA was the photooxidant (similarly as in the experiments mentioned in the previous section). The ratio of oxidative damage of two 5'-GG-3' sites was measured: that of the GG doublet situated distal to the protein-binding site vs. that at the proximal site.

Predictably, restriction endonuclease R.PvuII (a TATA-binding protein, which kinks the DNA) inhibited charge transfer. A particularly spectacular example was the interaction of DNA and wild type and mutant DNA methyltransferases, M.*Hha*I. Methyltransferase belongs to the base-flipping enzymes, i.e. it causes a rotation of the targeted nucleotide out of the double helix, thus gaining access to the base, cytosine, which becomes methylated. The flipped nucleotide is inserted into a "pocket" in the enzyme molecule. Its place (in the base stack "cavity") becomes occupied by glutamine 237 of the methyl transferase. Flipping destructs the hydrogen bonds that maintain the base-pairing and this results in inhibition of charge transfer in the examined M.*Hha*I-DNA complex. Such is the effect of the wild type enzyme illustrated in Fig. 2. The mutant enzyme contains a substitution of glutamine 237 to tryptophan.
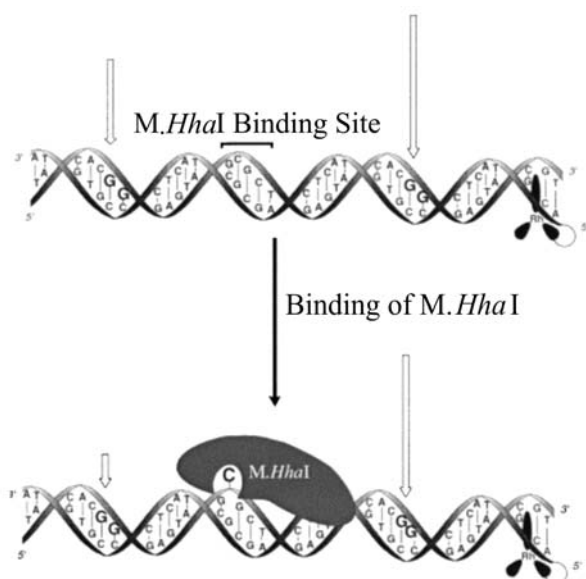

Fig. 2. Binding of methyltransferase M.*Hha*I to the duplex oligodeoxynucleotide inhibits charge transfer. Upper part of the figure shows no protein bound between the Rh intercalator Rh(phi)₂bpy']³⁺ and 5'-G-G-3' doublet in the distal position. Guanosine damage in that doublet is smaller than in the proximal one in relation to the intercalator, due to the distance effect. Hollowed arrows indicate the relative G damage. With methyltransferase bound to the binding site, the cytosine (C) residue is flipped into the catalytic site of the enzyme, thus disturbing the π-stack and, in consequence, charge transfer. Hence, the damage ratio of the two GG doublets becomes altered, as indicated by the diminished height of the distal arrow. Reproduced by permision of Elsevier from Rajski SR, Jackson BA, Barton JK (2000) DNA repair: models for damage and mismatch recognition. Mutat Res 447;1:49–72.

The aromatic heterocyclic part of this amino acid inserted into the "cavity" maintains the charge transfer in spite of the local destruction of the base stack. A transient tryptophan radical is observed [41]. This example illustrates the possible effects of protein-DNA complexes on charge transfer within DNA: both negative and positive modulation is possible.

It should be kept in mind that a reversed situation also takes place: redox potentials of metal containing proteins may considerably differ, depending on whether they are free or complexed to DNA [17] and this may be reflected in difference in affinity for DNA of more than 3 orders of magnitude.

Repair of cyclobutane pyrimidine dimers and charge transfer within DNA

One case where excitation by visible light of the enzyme's cofactor induces charge transfer in DNA is cyclobutane pyrimidine dimer (CPD) photolyase (CPDP). CPDs are a major photoproduct in DNA of cells exposed to UV-C radiation. They result from a photoinduced cycloaddition between two adjacent pyrimidines, usually thymines, on the same DNA strand. CPDP is a monomeric protein present in microbial as well as in some plant and animal organisms which repairs CPD in single-strand or double-helical DNA [45] by a process named DNA photoreactivation. All known photolyases contain a non-covalently bound flavin adenine dinucleotide (FAD) as redox cofactor [45]. The enzymatic activity depends on the photoexcited state of FAD in the two-electron reduced form, FADH, second (also non-covalently bound) FAD molecule is thought to act as an antenna to increase the absorption cross-section of the enzyme (review in [42]).

From the studies of Mees *et al.* [26] on the crystal structure of a photolyase complex with a CPD-like molecule, it can be assumed that in the damaged DNA, CPD is flipped out of the double helix into the active site of the enzyme and split there into two thymines which are then flipped back. It may be assumed that this structure mimics the structure of the photolyase-substrate complex during light-driven DNA repair.

In 2005, Weber [42] summarized the data on the photoreactivation process. He stated that in contrast with cooperation with other enzymes, where FAD is a redox-active cofactor in one- and two-electron transfer reactions, in the case of photolyase, both the ground-state (redox) and excited-state properties are exploited. In the photoreactivation process, the reduced FAD molecule absorbs in the blue and near UV light. It is assumed that the excited singlet state of FAD initiates a reductive cleavage of CPD by short-distance electron transfer to the DNA lesion. Then, back electron transfer from the repaired CPD restores the initial redox state of the cofactor.

Further examination of photoreactivation brought about more details. A review published in 2007 [20] gave the following sequence of events. Initiation of the catalytic cycle is by the "photoantenna" FAD molecule (resonance energy transfer to the other FAD molecule), followed by photoreduction through tryptophan residues, W382, W359 and W306 (intraprotein electron

transfer) to obtain the FAD molecule in the active form. In the *Escherichia coli* enzyme two tryptophans (W382 and W359) are located between FAD and W306; they mediate the electron transfer from W306 to the flavin as redox intermediates in a three-step electron hopping process [9]. The final repair step involves intermolecular electron transfer and bond breaking rearrangements. Finally, back electron return restores the photolyase molecule to its initial form.

Interestingly, DeRosa *et al*. [12] examined the CPDP driven photoreactivation using a similar experimental approach as in charge transfer studies in model molecules. They considered photoreactivation as a reaction triggered by electron transfer from the photoexcited FAD to the CP dimer and used gold electrodes modified with DNA duplexes containing a CP and *Escherichia coli* photolyase. In this system, the self-assembly of thiol-modified DNA duplexes on a gold surface yielded monolayers that served for electrochemical assays of DNA charge transfer. The experimental results were consistent with electron transfer to and from the flavin cofactor in the DNA-bound protein. The growing electrochemical signal reflected the increasing integrity of the DNA base stack with the enhanced degree of CPD repair, as confirmed by parallel high pressure liquid chromatography (HPLC) analysis of the CPD content. With the same method, the authors have shown that photolyase mutation at position 306 abolished the signal, thus confirming the role of tryptophan 306 in photoreactivation. As could be expected on the basis of model experiments described in the previous section, introduction of an abasic site below the CP dimer caused an inhibition of the redox pathway and prevented CPD repair.

Yet, there is no need for an enzyme to carry out photoreactivation of CPD. 10 years earlier, it was shown that repair of a CP dimer can be achieved by visible light in an enzyme-free system which enables charge transfer [10]. Here, the dimer was incorporated site-specifically in a 16-base pair DNA duplex and a metallointercalator was either non-covalently bound or covalently tethered to either end of the duplex. A Rh complex was used, Rh (9,10-phenanthrene quinine diimine)$_2$ 4,4'-dimethyl-2,2'-bipyridine^{+3} similar to those applied in other model systems for studies on charge transfer. The repair was equally efficient in a distance range of 16 to 26 angstroms between the intercalated rhodium complex and the CP dimer. Also, in agreement with the earlier data (cf. previous section) – disruption of the base pair stack inhibited the photoreactivation reaction.

Charge transfer and communication between the MutY glycosylase molecules

There are no data that would suggest photolyase activity with long distance charge transfer. Nevertheless, some redox active enzymes of the base excision repair group may make use of charge transfer for damage sensing, as proposed in an ingenious model by the Jacqueline K. Barton's group [7, 27, 37]. An example of enzyme that could act according to this model is MutY glycosylase, which contains a $[4Fe-4S]^{2+}$ cluster. This is an adenine (A) DNA glycosylase removing A residues

that were misincorporated opposite 7,8-dihydro-8-oxo-deoxyguanines, G, or C generated by ionizing radiation or reactive oxygen species. MutY removes mismatched adenines through a short-patch base excision repair pathway.

MutY properties were minutely checked in a model system similar to those described above [46, 47]. As predicted, with Ru-metallointercalator tethered to oligodeoxynucleotide duplex with or without single-stranded regions, MutY oxidation was mediated by the duplex only. Binding of MutY to DNA shifted the $[4Fe-4S]^{3+/2+}$ potential, activating the iron cluster toward oxidation, whereas more efficient MutY oxidation was facilitated by formation of G radical [46]. The radicals were generated by using ruthenium flash/quench chemistry, similarly to the model experiments on charge transfer mentioned in the previous sections. Since the lifetime of the G radical is relatively long (ms), it could also react with MutY due to mediation by the base pair π-stacking. The EPR spectroscopy confirmed that DNA-bound Ru intercalator and the G radical generated in the experiment could promote oxidation of the $[4Fe-4S]^{2+}$ cluster of MutY to $[4Fe-4S]^{3+}$ and its decomposition product $[3Fe-4S]^{1+}$.

The increased ease of MutY cluster oxidation in the case of G radical formation is explained in [47] as follows: the radical "serves to compete with fast back electron transfer to the DNA-bound ruthenium so that there is more time for oxidation of MutY. The guanine radical lifetime in the absence of MutY is on the millisecond time scale. Thus a DNA-mediated oxidation of MutY can occur with or without intervening guanines, but guanine radical formation, the first DNA product under oxidizing conditions, facilitates the oxidation of DNA-bound MutY".

Also, with absorption spectroscopy the full absorption difference spectrum was obtained with and without MutY bound to poly(dGC). The results were consistent with formation first of a G radical upon oxidative flash/quench of the Ru intercalator bound to poly(dGC) in the presence of bound MutY, followed by a second species, apparently, $[4Fe-4S]^{3+}$. Further, in a DNA duplex containing a 5'-GG-3' doublet and the Ru intercalator, G damage was observed due to oxidation from a distance through DNA-mediated charge transfer from Ru intercalator. Significantly, in the presence of MutY, this G damage did not take place.

The model of MutY-charge transfer employs the rules outlined in the previous sections and confirmed in the model systems described above: coupling of a redox pair by charge transfer through DNA duplex, sensitivity of charge transfer to disruptions in π-stacking, and redox status-dependent protein affinity to DNA. The difference in affinity enables the MutY molecule to bind to DNA when no charge transfer takes place, dissociate upon oxidation and reassociate at a new site. Thus, the enzyme molecules might more quickly redistribute onto regions of the genomic DNA that contain lesions. These features of the use of charge transfer by MutY to scan DNA for damage that would deform the base pair π-stacking are summarized in Fig. 3. It should be added that the same mode of operation is valid for another base repair enzyme with a [4Fe-4S] cluster, the bacterial endonuclease III.
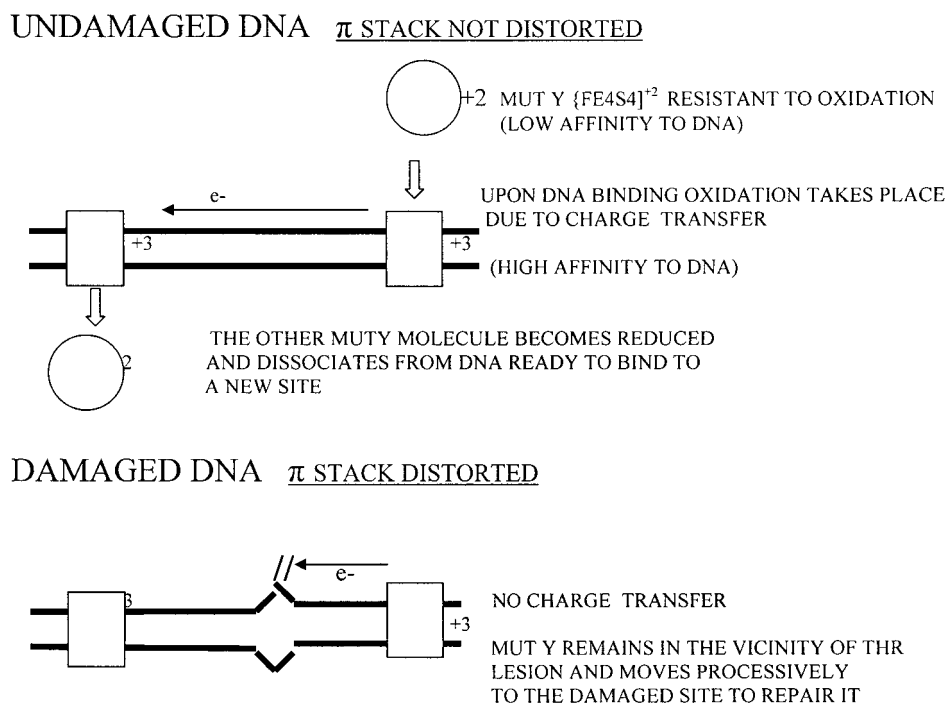
UNDAMAGED DNA   π STACK NOT DISTORTED

+2 MUT Y {FE4S4]⁺² RESISTANT TO OXIDATION
(LOW AFFINITY TO DNA)

e-

UPON DNA BINDING OXIDATION TAKES PLACE
DUE TO CHARGE TRANSFER

+3   +3

(HIGH AFFINITY TO DNA)

2   THE OTHER MUTY MOLECULE BECOMES REDUCED
AND DISSOCIATES FROM DNA READY TO BIND TO
A NEW SITE

DAMAGED DNA   π STACK DISTORTED

e-

NO CHARGE TRANSFER

+3

MUT Y REMAINS IN THE VICINITY OF THR
LESION AND MOVES PROCESSIVELY
TO THE DAMAGED SITE TO REPAIR IT

Fig. 3. Diagram showing how charge transfer facilitates redistribution of the repair enzyme and favours binding in another region of the nucleus in the vicinity of a DNA lesion that distorts the base pair π-stack. Please, note that in order to simplify the diagram, the arrows are drawn in only one direction, whereas in fact, association/dissociation and charge transfer take place in both directions. See text for further explanations.

Concluding remarks

Almost half a century ago, Albert Szent-Gyorgyi wrote a small monograph entitled "Introduction to submolecular biology" [39], where he presented a vision of the living cell as a molecular system working on the charge transfer principle. He had not much time left to bring sufficient experimental support to his ideas. His theory was admired as ingenuous and opening new horizons but criticized as too fantastic, unrealistic or too difficult to prove. This review shows that at least in some cases, charge transfer has a biological significance.

Apart from the base repair enzymes, some other roles have been assigned to charge transfer in DNA *in vivo* (reviewed in [27]). These comprise, among others, dissociation of the redox-sensitive transcription factors (e.g. the p53 tetramer [4]) from promoter sequences or "funneling" the oxidative DNA damage into non-coding dCG sequences [15]. Recently, Elson [14] proposed a model concerning the role of DNA-mediated charge transfer in a coherent initiation of replication in replicon groups as well as coordination of gene transcription during embryonic development. The model mostly is based on theoretical grounds and circumstantial evidence, nevertheless, it presents an interesting alternative to the current views on the mechanisms of cellular processes.

Protein charge transfer chemistry also is rapidly developing, this topic, however, is beyond the scope of this paper. Further development of research on charge transfer in biology will need an interdisciplinary approach bringing close chemistry, physics, informatics and cellular as well as molecular biology, not an easy task, but a fascinating target.

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