mantle (*8*). The water decreases the melting temperature, resulting in partial melting. Some high-pressure partitioning experiments suggest that, when partial melting occurs in subducted crustal materials, hollandite can preferentially incorporate several incompatible elements (K, Pb, Sr, light rare earth elements, and so forth) but is not likely to be a host for uranium and heavy rare earth elements, relative to the coexisting melt (*9*). Therefore, the stability of hollandite will strongly influence trace element geochemistry of magmas produced in the deep mantle as well as alkali transport processes in the transition zone and the lower mantle.

Detailed studies of shocked meteorites may provide further evidence for dense minerals stable in the deep mantle. Other alkali-host minerals such as calcium ferrite–type $NaAlSiO_4$ and a related structural phase (*1*, *10*) may be found in shocked meteorites. Together with comprehensive experimental studies on the melting relations and trace element partitioning between the alkali-host minerals, silicate melt, and fluid at the pressure-temperature conditions of the transition zone and the lower mantle, they will shed light on the behavior of alkali elements in the deep mantle and on crust formation processes.

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PERSPECTIVES: MOLECULAR BIOLOGY

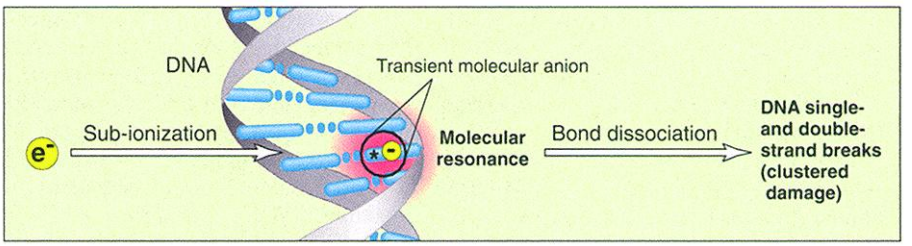
A Sting in the Tail of Electron Tracks

Barry D. Michael and Peter O'Neill

It almost seems paradoxical that the molecular damage induced by high-energy ionizing radiation—with energies typically in the range of millions of electron volts (eV)—is actually the result of a multitude of low-energy events. Most of these are small transfers of energy (on the order of 10 eV) deposited by low-energy electrons that are set in motion around the tracks of energetic charged particles (*1*). Little is known about the damage induced by low-energy electrons, except in the simplest molecular systems. Understanding how low-energy electrons damage more complex molecules such as DNA should ultimately lead to explanations for many aspects of the biological actions of radiation. A clearer picture of the basic mechanisms (and potentially new chemical pathways) that induce DNA damage should also benefit the development of improved radiotherapy strategies for treating diseases such as cancer.

Recently, a number of studies have started to address this question by, for example, measuring single- and double-strand breaks (SSBs and DSBs) in DNA after exposure to monoenergetic photons (*2*, *3*) or electrons (*4*). Boudaïffa *et al.* (*5*), reporting on page 1658 of this issue, have lowered the energy of electrons incident on DNA to 3 eV (an electron energy far below that used in previous studies). The authors find that low-energy electrons, as they slow down to energies too low to cause ionization, still have a surprising "sting in the tail" of their tracks. Their findings challenge the conventional notion that damage to the genome by ionizing radiation is only induced by electrons with sufficient energy to ionize DNA.

B. D. Michael is in the Cell and Molecular Biophysics Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex HA6 2JR, UK. P. O'Neill is in the DNA Damage Group, MRC Radiation and Genome Stability Unit, Harwell, Didcot, Oxon OX11 ORD, UK. E-mail: michael@graylab.ac.uk, p.oneill@har.mrc.ac.uk



Tracking DNA damage. Low-energy electrons produce complex DNA damage. Electrons that have slowed down to energies too low to induce ionization of DNA undergo resonant attachment to DNA bases (blue) or to the sugar-phosphate backbone. The transient molecular anion formed (*) then reacts further to break one or both strands of the DNA (*5*). One electron can in this way produce a multiple lesion, thus amplifying the clustering of damage induced in DNA by a single radiation track (*1*). Clustered lesions are difficult for the cell to repair and are therefore likely to lead to permanent damage to the genome (*8*).

Damage to the genome of a living cell by sparsely ionizing radiation, such as hard x-rays, is about one-third "direct" (from energy deposited in the DNA and its closely bound water molecules) and two-thirds "indirect" (from free radicals produced by energy deposited in water molecules and other biomolecules located close to the DNA). Studies with scavenger molecules such as dimethylsulfoxide (*6*) indicate that almost all of the indirect damage to DNA is due to attack by the highly reactive hydroxyl radical (•OH). Furthermore, it seems that the reducing counterparts of •OH (principally the hydrated electron, e_{aq}^-) are relatively ineffective, especially at inducing DNA strand breaks.

The radiation chemistry of water is reasonably well understood, as is the chain of events leading from the initial production of water radicals to indirect DNA damage (*7*). In particular, it is clear that induction of a DSB by a single track of radiation is the result of a localized attack by two or more •OH radicals. Alternatively, damage may be caused by a hybrid attack where one strand is damaged by an •OH radical and the other strand sustains direct damage within about 10 base pairs of the •OH attack. The closely spaced depositions of energy along the radiation tracks are known to generate such clusters of hybrid damage. Where more than two elementary lesions are induced in close proximity by •OH or by direct effects on the DNA, a complex lesion can develop. This has important consequences for biological effects because such damage presents a greater challenge to the DNA repair machinery of the cell (*8*).

Less is known about the mechanisms of direct damage by low-energy electrons. However, the report by Boudaïffa *et al.* (*5*)

reinforces the view that a substantial proportion of DSBs are initiated by single energy absorption events. Earlier investigators demonstrated that induction of a DSB by a single •OH radical was a minor contributor to indirect damage, and they attributed the damaging effects to radical transfer between DNA strands (*9*). Boudaïffa and co-workers now propose a similar mechanism for low-energy electrons. They suggest that SSBs arise on each strand of the DNA after interaction with a single electron (*5*). Taken together, these findings indicate that transfer of radicals or energy between DNA strands may play an important part in amplifying the complexity of DNA lesions over and above the level set by the physical clustering of events along the radiation tracks.

Several mechanisms have been put forward to explain radical migration in DNA: swing-over of a sugar radical between the damaged and undamaged strands (*9*), attack by a base radical on a neighboring sugar (*7*), and radical reactions between adjacent bases (*10*). In general, the amplified damage follows the initial oxidative damage by •OH. In the mechanism proposed by Boudaïffa and colleagues—called "resonant attachment"—sub–ionization energy electrons attach to DNA, resulting in the formation of a transient molecular anion (see the figure). This is followed by either electron autodetachment (when no damage results) or bond dissociation. The latter results in either breakage of one strand or the modification of a DNA base, which leads to release of a radical fragment that can then migrate to and break the other strand.

The threshold energies for strand-break induction by photons and electrons are around 7 eV, well below the energy levels required for ionization (*2, 3, 5*). However, a comparison of the energy dependence of electrons with that of photons reveals an interesting difference: At an energy level of about 13 eV, electrons show a dip in strand-break efficiency. Below this energy level, resonant attachment is the dominant mechanism of DNA damage, whereas above it, nonresonant excitation is the primary cause of DNA strand breaks (*5*). The efficiencies of these low-energy interactions at inducing SSBs and DSBs per incident electron or photon are low—for example, 10^{-4} to 10^{-3} for 10-eV electrons (*5*) and 10^{-3} to 10^{-2} for 10-eV photons (*3*). However, this must be viewed in the context of the relatively high frequency of low-energy deposition events in a single radiation track (*1*).

There is currently much interest in understanding the effects of low-dose radiation on cells and molecules and how these effects relate to the risks for humans exposed to low-level radiation (*11*). Most existing knowledge of radiation risk comes from follow-up studies of atomic bomb survivors who received extremely high doses of radiation over very short time periods. Extrapolating these risk data to calculate risk for the very low doses that apply to typical environmental and occupational exposures requires the application of mathematical models (such as the linear-no-threshold model). But little is actually known about the biological effects of low-dose radiation. At the heart of the problem lies the need to unravel the actions of a single track of radiation on a cell (*12*). For example, at environmental levels of exposure, all cells in the body only "see" electron tracks at intervals averaging several months. A knowledge of how individual electron tracks interact with cells, their DNA, and other molecular constituents should lead to more refined models for calculating human risk at the exposure levels of most concern to the public and to regulatory agencies. Monochromatic beams of low-energy radiation are providing selective and specific ways to unravel the molecular mechanisms of damage induction. Intensive efforts to exploit the potential of low-energy electrons are under way at U.S., Canadian, European, and Japanese laboratories.

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PERSPECTIVES: SIGNAL TRANSDUCTION

The Calcium Entry Pas de Deux

Michael J. Berridge, Peter Lipp, Martin D. Bootman

Calcium ions (Ca^{2+}) are universal secondary messengers that are key players in many cellular signal transduction pathways (*1*). There are two sources of these signaling cations in the cell: internal stores that release Ca^{2+}, and channels in the plasma membrane that open to allow external Ca^{2+} to flow into the cell. Internal Ca^{2+} stores—located in the sarcoplasmic reticulum of muscle cells and the endoplasmic reticulum (ER) of other cells—have a limited capacity for Ca^{2+} storage, and so they have to be replenished through entry of Ca^{2+} from the external environment. Putney (*2*) first recognized that the processes of emptying and replenishing internal Ca^{2+} stores must be linked. Somehow, empty Ca^{2+} stores activate store-operated channels (SOCs) in the plasma membrane that then allow Ca^{2+} ions to enter the cell. Putney termed this mechanism "capacitative calcium entry" (CCE) because the stores behave like a capacitor in an electrical circuit. When Ca^{2+} stores are replete the SOCs are closed, but once the stores discharge their contents, the SOCs open and Ca^{2+} ions enter the cell.

Since the first observations of CCE, there has been intense debate about the identity of SOCs and the way in which the ER Ca^{2+} stores communicate with them. Evidence is emerging in support of the popular conformational-coupling hypothesis (*3*, *4*), which proposes that information is transferred through a direct interaction between the inositol 1,4,5-trisphosphate receptor ($InsP_3R$) in the ER and SOCs in the plasma membrane (see the figure). On page 1647 of this issue, Ma *et al.* (*5*) now present evidence showing that CCE depends on the close proximity of the ER and plasma membranes and that $InsP_3Rs$ partner with SOCs to control Ca^{2+} entry through the plasma membrane.

The $InsP_3R$, embedded in the ER membrane, is a good candidate for this molecular coupling job. Its amino-terminal domain is large enough to span the 10-nm gap that separates the ER and the plasma membrane. Meanwhile, its carboxyl-terminal region forms a channel in the ER membrane, out through which flow Ca^{2+} ions in response to the signaling molecule inositol trisphosphate ($InsP_3$). It is this $InsP_3$-induced release of Ca^{2+} that normally depletes internal stores of the cation and results in activation of CCE.

Detection of light by photoreceptor cells in the compound eye of *Drosophila* activates a Ca^{2+}-entry channel known as TRP (transient receptor potential) in the photoreceptor cell membrane. Much excitement has surrounded the realization that mammalian cells express homologs of

The authors are at the Laboratory of Molecular Signalling, Babraham Institute, Babraham, Cambridge CB2 4AT, UK. E-mail: michael.berridge@bbsrc.ac.uk