Basic Radiation Chemistry and Radiation Chemistry of DNA Damage

John F. Ward
Radiology Department, Univ. Ca. San Diego
jfward@ucsd.edu

Ernest Rutherford

Nobel for physics 1908, first to split the atom in 1917.

"All science is either physics or stamp-collecting"

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Time Scale (in seconds) of Radiation Action

10^{-15} Radiation energy is deposited
Ionizations occur
10^{-12}

10^{-9} Primary Radical reactions

10^{-6} Oxygen reacts with radicals

10^{-3} Permanent products are formed

10^{0} Cell begins to respond biochemically

10^{3} Enzymatic repair
Mutation/transformation occur
10^{6} Cell death scored
Cancer appearance

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Mechanisms of Radiation Damage to Cells: Sources of Experimental Data

- *In vitro* Model compounds irradiated in solution or alone
- *In vivo* Irradiation of living cells
- *In silico* Computer Models of "biophysical" processes

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Biophysical models

Important variables are often not accommodated, e.g.

Effects of oxygen

Presence of sensitizers or protectors

Identities of radiation products

Amounts of each damage

Response of cells to the damage

Effects of cell cycle

Genetic differences between cells

Conclusion: These models are limited in their ability to predict effects of variables.

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In silico - Biophysical Models supported by DOE and the European Union

See: Physical and Chemical Mechanisms in Molecular Radiation Biology" (W. Glass and M.N. Varma eds.) Plenum Press, (New York) (1991). Basic Life Sciences 58 (1991).

S. Curtis Mechanistic Models pp. 367-382

L.A. Braby Phenomenological Models pp. 339-361

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Sidney Brenner, *Science*, July 17, 1992

Those who prefer the airy realm of theory to the area of decisive experiment aren't necessarily doing so by choice: I always say it's important to distinguish between chastity and impotence.

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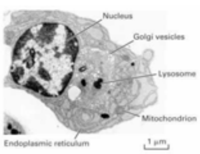
Contents of Typical Cell

From B. Alberts, Molecular Biology of a Cell, 4th Edition, Garland Press, 2002.

Cell Size 4 x 10^{-9} cm^{-3}, Density 1.15 g/cm^3 – Mass 4.6 x 10^{-9} g



	%
Water	70
Inorganic Ions	1
Small Metabolites	3
Proteins	18
RNA	1.1
DNA	0.25
Phospholipids	3
Other lipids	2
Polysaccharides	2

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Water Radiolysis

H_2O radiation → H_2O^+ + e^-
(ionization) (unstable)

H_2O^+ + H_2O → H_3O^+ + $^{\bullet}OH$

e^- + bulk water → $e\,(H2O)_6^-$
(hydrated electron)

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Radical Damage to Intracellular Molecule (RH)

RH —ionization→ RH^+ (1)

H_2O —ionization→ H_2O^+ → $OH^{\bullet}$ (2)

RH^+ → $R^{\bullet}$ + H^+ (3)

RH + $OH^{\bullet}$ → $R^{\bullet}$ + H_2O (4)

$R^{\bullet}$ + O_2 → $RO_2^{\bullet}$ (5)

$R^{\bullet}$ + GSH → RH + $GS^{\bullet}$ (6)

---

1 and 2 occur within 10^{-12} s.

3 and 4 in 10^{-9} s.

5 and 6 in 10^{-5} s.

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Techniques used in Radiation Chemistry.

Pulse radiolysis

Electron Spin Resonance

Product analysis

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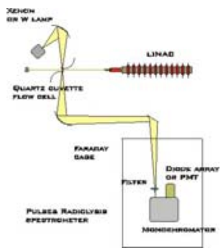
Pulse Radiolysis

Equipment



Source of Rate Constants for Reaction of Free Radicals

UNIVERSITY OF NOTRE DAME

Notre Dame Radiation Laboratory,
Radiation Chemistry Data Center

http://www.rcdc.nd.edu/index.html

Typical Rate Constants – $^{\bullet}OH$ radicals

	Liters per mole per second
DNA bases	5×10^9
deoxyribose	1.2×10^9
Amino acids – glycine	1.7×10^7
tryptophan	1.3×10^{10}
Ethanol	1.3×10^9
Dimethyl sulfoxide	6.5×10^9

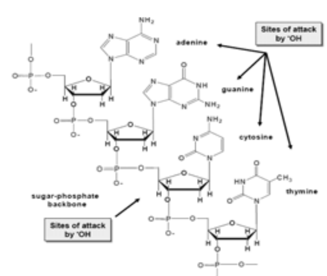
Typical Rate Constants – $e^-_{(aq)}$

	Liters per mole per second
Oxygen	1.3×10^{10}
DNA bases	5×10^9
deoxyribose	1×10^7
Amino acids - glycine	1×10^7
tryptophan	3.2×10^8
cystine	1.1×10^{10}

Typical Rate Constants – (O_2^-)

	Liters per mole per second
DNA	$<10^6$
Glycine	<0.42
Tryptophan	<24
Cystine	<0.4
Superoxide Dismutase	3.2×10^9

$^{\bullet}OH$ radical attack on DNA



Miral Dizdaroglu

Reactions of Hydroxyl Radicals

1. Hydrogen atom abstraction

$RH + {}^{\bullet}OH \rightarrow R^{\bullet} + H_2O$

2. Addition to a double bond

```
H  H                      H  H
 V                          V
 C                          C-OH
 ||      +    •OH   →       |
 C                          C•
 Λ                          Λ
H  H                      H  H
```

3. Oxidation

$M^{+} + {}^{\bullet}OH \rightarrow M^{++} + OH^{-}$

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DNA base alterations produced by $^{\bullet}OH$

Fuciarelli et al., Int. J. Radiat. Biol 58; 397.

Base Alteration	% of total base damage
8-hydroxyguanine	43
8-hydroxyadenine	7
Formamidopyrimidine-adenine	3
Formamidopyrimidine-guanine	6
Thymine glycol	27
Cytosine glycol	14

Also Double lesions *Box et al., Free Radicals Biol. Med. 31; 856.*

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Characteristics of Single Strand Breaks (SSB)

- Are induced by both direct ionization (35%) and OH radicals (65%). *Roots and Okada Int. J. Radiat. Biol. 21 329.*
- 15 % of OH radicals reacting with DNA cause SSB. *Scholes et al. J. Molec. Biol. 2 379.*
- 30% of directly ionizing events cause SSB. *Raskasovskiy et al Radiat Res. 153 436.*
- A base is released at the site of each SSB. *Ward and Kuo 66 485.*
- The termini of SSB are 5' phosphates and 3' phosphoglycolates (35%) and 3' phosphates (65%). *Henner et al. J.Biol. Chem. 258 713.*
- 70% of SSB are overt breaks, 30% are alkali labile sites. *LaFleur et al. Int. J. Radiat.Biol. 30 223.*
- Alkali labile (abasic) sites are not the same as acid induced abasic sites. *LaFleur et al. Int. J. Radiat.Biol. 35 241.*
- 1 Gray produces 1000 SSB per cell Elkind and Redpath, In Cancer, A Comprehensive Treatise 6 51.
- Most SSBs are repaired with a half-life of 3-4 min.

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Ratio of base damages to SSB

Milligan et al. Radiat. Res. 146 436.

Supercoiled plasmid DNA used as target.

SSB measured as relaxed open circle

DSB measured as linear

Base damage measured as increase in strand breaks after treatment with base damage specific enzymes.

Base damage produced by OH radicals are ≈ 2.6 times as frequently as SSB.

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Direct Ionization of DNA

Initial events (observed at 4ºK) *e.g. Debije and Bernhard, J. Phys. Chem. B 104, 7845.*

Electron loss leads to guanine cation radicals and deoxyribose radicals.

Electron gain leads to pyrimidine anion radicals.

Products, (after warming and dissolution):

Bases, same types of alterations as those from $^{\bullet}OH$ radical attack. *Swarts et al. Radiat. Res. 145, 304.*

30% of directly ionizing events cause SSB. *Raskasovskiy et al Radiat Res. 153, 436.*

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What have we learned from *in vitro* radiation chemistry?

Structures of altered bases.

Strand break end-groups.

"Direct" and "Indirect" mechanisms cause the same types of damage.

Relative yields of these damages.

Reactions in which oxygen or radiation modifiers might act.

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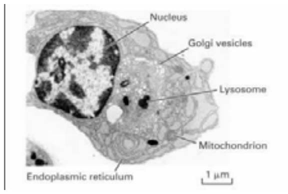
In vivo radiation chemistry



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Ionizations in a Typical Cell

Cell Size 4 x 10^{-9} cm^{-3}, Density 1.15 g/cm^3 – Mass 4.64 x 10^{-9} g

	%	picograms	Ionizations/Gray
Water	70	3250	1,000,000
Inorganic Ions	1	46	
Small Metabolites	3	139	
Proteins	18	835	260,000
RNA	1.1	51	16,000
DNA	0.25	12	3,600
Phospholipids	3	35	10,800
Other lipids	2	23	7,200
Polysaccharides	2	23	7,200

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Assessment of Significance of Damage in a protein (as an example)

Protein of Mol. Wt. 100,000 — 20,000 molecules per cell.

Mass of protein $= 10^5 \times 2 \times 10^4$ Daltons
$= [10^5 \times 2 \times 10^4 / 6 \times 10^{23}] \times 10^{12}$ picoograms
= **3.3×10^{-3} pgm**

Energy deposited therein

1 Gray = I Joule per kgm. ≡ 6.25×10^{15} eV per gm

~ 20 eV are needed to cause an ionization.

1 Gy causes **3.1×10^{14}** ionizations per gram

Number of ionizations in 3.3×10^{-3} picograms would be $3.1 \times 10^{14} \times 3.3 \times 10^{-3} \times 10^{-12}$

= **1**

So from 1 Gray the damage produced by direct ionization is:

1 altered site in the 20,000 copies of this protein

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Assessment of relative contributions of direct Ionization and ˙OH Radicals in Cells

Cell targets react with ˙OH;

RH + ˙OH → (1)

If a compound is added which competes with the target for ˙OH, the amount of damage to the target will be reduced:

DMSO + ˙OH → (2)

Fraction of ˙OHs reacting with RH:

$$\frac{k_1[RH][^{\cdot}OH]}{k_1[RH][^{\cdot}OH] + k_2[DMSO][^{\cdot}OH]}$$

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Effect of scavengers on Cell Survival

J.D. Chapman et al. Radiat. Res. ***56****; 291-306.*

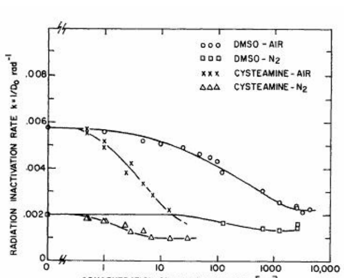

FIG. 1. The effect of various concentrations of DMSO and cysteamine on the radiation inactivation rate of air-saturated and hypoxic Chinese hamster cells.

Effect of ˙OH scavenger on chromosome aberration yield

Littlefield L.G. et al. Int. J. Radiat. Biol. ***53****; 875-890.*

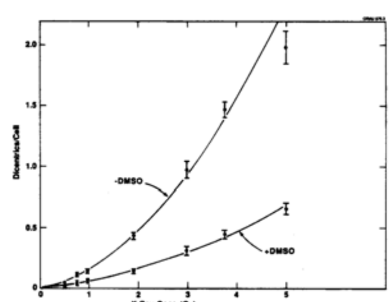

Figure 2. Dose–response relationships for dicentric induction in lymphocytes exposed to X-radiation in absence or presence of DMSO. Dicentric $cell^{-1}$ data fitted to linear-quadratic dose–response function.

$^{\bullet}$OH Radical Scavengers Reduce Biologically Significant Damage

1964 **Bacteria**
Johansen, I. and Howard-Flanders, P., Radiat. Res. 24: 184-189.

1972 **Mammalian Cells**
Roots, R. and Okada, S., Int. J. Radiat. Biol., 21; 329-342.
1973 *Chapman, J.D. et al., Radiat. Res. 56; 291-306.*

1979 **High LET**
Chapman, J.D., Radiat. Environ. Biophys. 16; 29-41.

1984 **Transformation**
Yang T.C. and Tobias, C.A., Adv. Space Res. 4; 207-218.

1987 **Mutations**
Corn B.W. et al., Radiat. Res. 109; 100-108.

1988 **Chromosome Aberrations**
Littlefield, L.G., Int. J. Radiat. Biol. 53; 875-890.

1995 **DNA double strand breaks – α particles**
deLara, C.M. et.al., Radiat. Res. 144; 43-49

2000 **Cell killing from ^{125}I decays**
Walicka, M.A. Radiat. Res. 154; 326-30.

2001 **Genomic Instability**
Limoli, C.L. et al. 31; 10-19

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Conclusions of authors:

65 % of most biological effects are caused by $^{\bullet}$OH radicals

½ maximum protection is provided by 0.13M DMSO

$^{\bullet}$OH radicals cause base damage and strand breaks in DNA. However:

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Other evidence suggests the unimportance of $^{\bullet}$OH

- Treatment with H_2O_2 does not kill cells (*Ward, Blakely and Joner, Radiat Res.103:383-92*).
- There are high endogenous levels of oxidized bases (≈2.4 -48 Gy). *Collins et al. Arch Biochem Biophys. 423 57-65*
- α-particles produce a lower yield of $^{\bullet}$OHs than γ-rays, but are more effective in killing cells (*Objection raised by T. Alper*).

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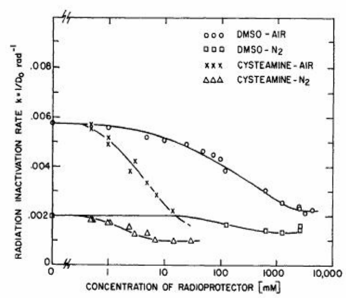
What else can these data tell us?



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*J.D. Chapman et al. Radiat. Res. **56**; 291-306.* J.F.Ward, 2007

Life Time of $^{\bullet}$OH in mammalian cells

Fraction of $^{\bullet}$OHs reacting with target $= \dfrac{k_1[RH][^{\bullet}OH]}{k_1[RH][^{\bullet}OH] + k_2[DMSO][^{\bullet}OH]}$

When the amount of scavengeable damage is reduced by a factor of 2,

$$k_1[RH][^{\bullet}OH] = k_2[DMSO][^{\bullet}OH],$$

Thus, the half life of the $^{\bullet}$OH radical in its reactions with DNA intracellularly can be determined:

$$t_{½} = \ln 2/ k_2[DMSO]$$

So that if $[DMSO]_{½} = 0.13$ M and $k_2 = 6.5 \times 10^9\ LM^{-1}s^{-1}$

$t_{½}$ **= 8.2 x10^{-10} s**

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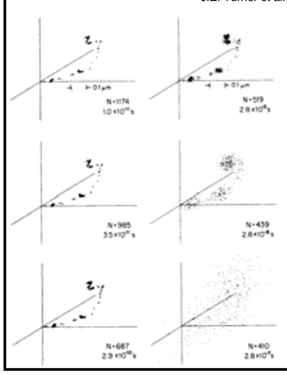
Evolution of an electron track

J.E. Turner et al. Radiat. Res. 96; 437.



ession of reactive rmediates formed after osition of radiation energy.

ges in location and numbers as nction of time.

eactive species

nber present

ar scavenging ~ 8 x 10^{-10} s

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Radiation Chemical Concepts of early distributions of radicals

Entity	Energy	Size	Energy (%)	Events (%)
Spur	<100eV	4nm (diam.)	80	**95**
Blob	<500eV	7nm (diam.)	20	5
Short tracks	500-5,000eV			
DNA		2mm (diam)		
nucleosome		5.7nm thick		

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Energy Deposition events

From Table II of *Pimblott and Mozumder J. Phys. Chem. 95 7928.*

Numbers of •OH per event	% of total events
1	54.4
2	24.8
3	8.0
4	2.3
5	1.3
6	0.4

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Distance ·OH moves before reacting in mammalian cells

The diffusion of a particle in 3 dimensions is $2.45\,[Dt]^{0.5}$ *(ref 1)*

For ·OH, D, the diffusion constant $= 2 \times 10^{-5}\ cm^2\ s^{-1}$ *(ref 2)*

Mean distance ·OH moves in mammalian cell before reacting with DNA is:

$2.45\,[2\times10^{-5} \times 8.2 \times 10^{-10}]^{0.5}$ cm

= ~3 nm.

1. *A. Einstein, Investigations on the Theory of Brownian Movement, ed. R. Fürth, translated by A.D. Cowper (1926, reprinted 1956); Einstein, Collected Papers, vol. 2, 170-82, 206-22*
2. *J.E.Turner Atoms, Radiation, and Radiation Protection, 2nd ed. New York: Wiley-Interscience, 1995. Table 13.2)*

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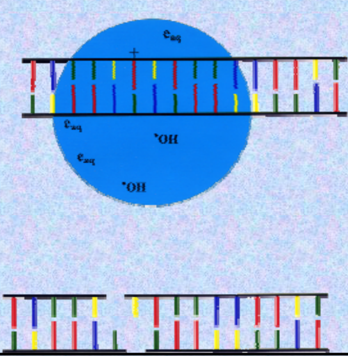
Energy Deposition Event on top of DNA



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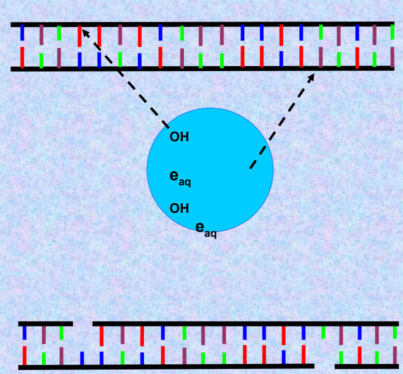
Diffusion of ·OH radicals to DNA



Locally
Multiply
Damage
Sites

Combination
Lesions
Underlying
Single
Track
Event
Radiation
Signatures

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Relative LMDS Frequencies in DNA in Solution

J.R. Milligan et al. Int. J. Radiat. Biol. 76 1475-1483

Locally Multiply Damaged Site	Percent total LMDS
DSB	20
Oxy-purine complex	33
Oxy-pyrimidine complex	46

Enzymes used to cut at base damaged sites, formamidopyrimidine glycosylase (oxy-purine) and endonuclease III (oxypyrimidine) can be inhibited by neighboring damage. Therefore the yields of base damaged sites will be higher.

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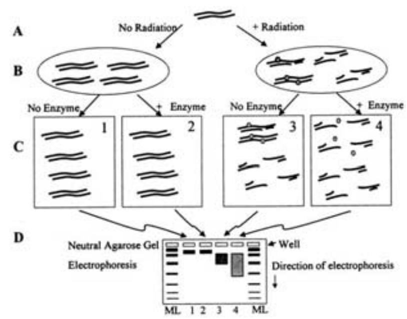
LMDS containing Base Damage assessed in human cells

B. Sutherland et al. Proc. Natl. Acad. Sci. USA 97, 103-108



PNAS

Relative LMDS Frequencies in Human Cells

B. Sutherland et al. Radiat. Res. 157, 611–616

Locally Multiply Damaged Site	% Total
DSB	27.5
Oxy-purine complex	27.8
Oxy-pyrimidine complex	24.7
Abasic site complex	20

Note: Values are approximate since there are cross-sensitivities to the enzymes, and, cutting by the enzymes is inhibited by proximal damage (e.g. Weinfeld M. et al. Radiat Res. 156 584-9)

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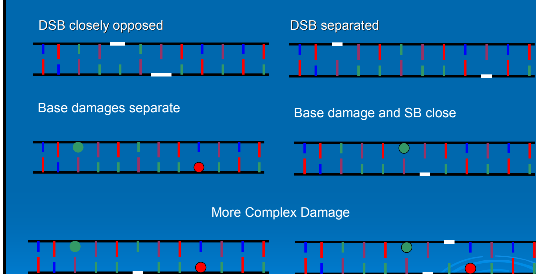
Examples of Multiply damaged sites



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Variables of Multiply Damaged Sites

Size - distance over which damage spread

Complexity – numbers of damages per site

Composition – variety of base damages and SSB

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Spacing of constituent SSBs: DSB production by alternate method

Limoli and Ward Radiat. Res. 134 160-9.

DNA labeled with 5-bromouracil.

DNA loaded with Hoechst dye 33258.

Exposed to UVA light; 360 nm (3.4 eV).

Measure DSBs and cell killing.

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Hoechst 33258 binding to DNA

Kakkar et al. J. Biomolec. Struct. & Dynam. 23 27

The Hoechst 33258-DNA complex. The drug molecule is shown highlighted in green.

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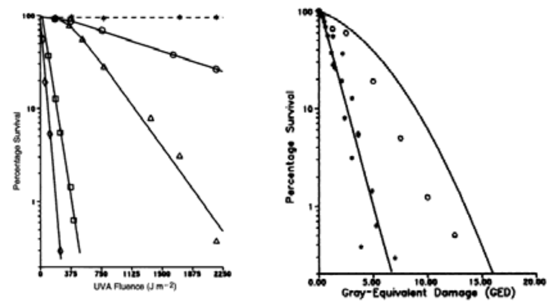
DSB produced by photolysis(Dye, BrdU, UVA)

Limoli and Ward Radiat Res. 138 312.



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Conclusions from photolysis experiment

- DSBs can be produced by agents other than ionizing radiation.
- Not all DSBs are equally effective in killing cells.
- DSBs which are more closely opposed are more lethal.
- Some ionizing radiation induced DSBs are non-lethal.

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Potential Consequences of DSBs

A. Repair Base sequence unchanged

B. Rejoining Base sequence incorrect

C. Joining/Misrepair Deletion

D. Non-rejoining Deletion

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DSB and mutations

HPRT gene in hamsters is 36 kbp in length

648 bp are in exons

Double strand break in an exon can lead to a point mutation.

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Relationship between yields of point mutations and DSBs

Yield of point mutations = 8 per 10^6 cells per 2 Gy.

(T. Morgan et al. Mutat Res. 232 171)

Size of exon 648 base pairs

Total DNA in exons in 10^6 cells = 6.48×10^8 base pairs

Yield of DSB is 5.8×10^{-3} per megabase pairs per Gy

(M. Löbrich et al. P.N.A.S. 92 12050)

2 Gy causes $5.8 \times 10^{-3} \times 6.48 \times 10^2$ DSB in target exons

= 8 DSB in target exons

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Do all DSBs in exons yield point mutations?

The yields are equal. But DSBs with distant SSBs would be expected to be accurately repaired.

Other damage, i.e., LMDS in which base damage is present, are present in several fold higher in yield.

Repair and rejoining of these kinds of damage could also lead to a point mutations.

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Are all DSB the same?

a. Measurements of DSBs are carried out after stripping away all other cellular material.
Such material (e.g. nucleosomes) may act to hold the ends of DSBs in register enabling their rejoining.

b. Removing DNA from cell may also break hydrogen bonded base pairs in between SSBs on opposite strands.
The hydrogen bonding could serve to hold the ends together favoring fast rejoining.

c. DSBs measured by these means are greater than the yields existing in cells.

d. Yields measured by biochemical methods (P.F.G.E., Elution, Centrifugation, etc.) are 37 per cell, but *in situ* by premature chromosome condensation (PCC) are 4-6 per cell.
Cornforth M. p. 563 in "DNA Damage and Repair" (ed. Nickoloff and Hoekstra) Humana Press.

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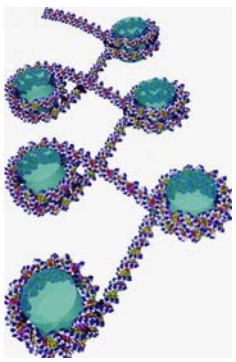
DNA and nucleosomes

Friedland, W. et al.Rad. Res 150 170-182



Chromatin fiber with zigzag structure.
Blue: phosphate groups; white: sugar group atoms; green, yellow, red, violet; base atoms of adenine, guanine, cytosine and thymine, respectively; turqoise; histones

The attraction between DNA (polyanion) and the multiple positive charges on the histones can serve to keep the two ends of a DSB in register, aiding correct rejoining.

Breaks occurring in the linker region may not be so stabilized and may be more prone to separate from their partner end.

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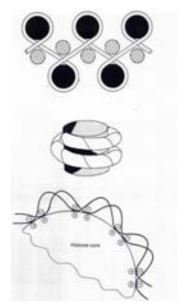
Nucleohistone packaging

From: *K.E. van Holde, Chromatin, Springer Verlag.*



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Three types of DSB

1. In the linker region – the ends readily separate.
2. Held together by holding the ends in register on histones.
3. Held together by hydrogen bonding between complementary bases.

Biophysical DSB measurement techniques detect all three types.

Within the cell they can have different outcomes.

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DSB rejoining

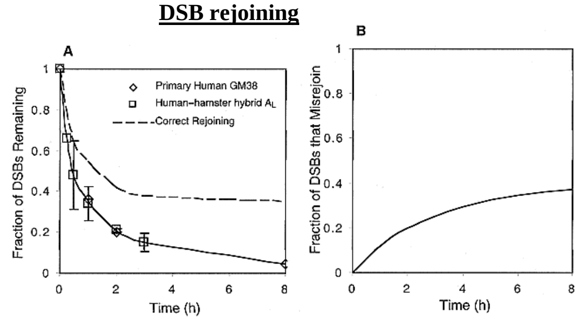

FIG. 4. Total rejoining of radiation-induced DSBs after 80 Gy X irradiation. DSB rejoining in G_1-phase A_L cells and G_0 GM38 cells (panel A) was determined by employing a standard pulsed-field gel electrophoresis assay (*38*) in which the fraction of DNA released from the well is used as an indicator of the relative number of DSBs present in the sample.

Fouladi et al. Radiat. Res. 150, 619-26 (1998).

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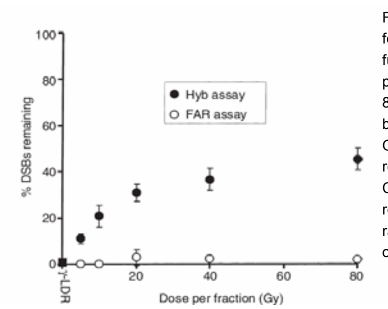
Effect of dose on correct rejoining.

M. Kühne et al. Radiat. Protec. Dosim.99,129–132



Filled circles: Frequencies for correct rejoining as a function of X-ray dose per fraction (total dose 80Gy). 24 h incubation between doses.
Open circles: Total rejoining.
Closed square: correct rejoining after low dose rate γ-radiation (80Gy over 14 days – 0.24 Gy/h).

J.F.Ward, 2007

What have we learned from in *vivo* chemistry

a. OH Radicals have short lives and travel short distances.

b. OH Radicals react close to where they are produced.

c. The clusters of ionization from radiation give rise to multiply damaged sites.

d. There is a variety of MDS.

e. All DSBs are not alike.

J.F.Ward, 2007

Conclusions about DSBs

- Many techniques for measuring DSBs recruit lesions whose ends do not separate within the cell.
- From the chemistry by which they are produced three classes of DSBs are predicted.
- The DSBs whose ends become available for misrejoining may be only 20% of the measured yields (5-6 $cell^{-1}Gy^{-1}$).
- DSBs whose ends do not separate may still be detrimental; as a source of point mutations.
- LMDS containing base damage do not give rise to DSBs but can be a source of point mutations.

J.F.Ward, 2007

Damage produced by 1 Gray

1,000 single strand breaks
3,000 damaged bases
37 double strand breaks (measured by harsh techniques)
5 actual double strand breaks (mild techniques)
190 multiply damaged sites

J.F.Ward, 2007

In contrast, UV damage

Sun exposure at 600m. produces thymine dimers in yield equivalent to
14 $Jm^{-2}s^{-1}$ of 253.7 nm light

Klocker et al., Eur. J. Biochem 142, 313.

This corresponds to a thymine dimer yield of
1.2×10^5 per cell per hr.

Ward, Radiat. Res. 152 104.

J.F.Ward, 2007

Some Numbers

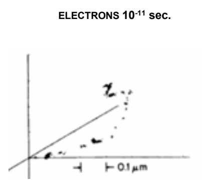
In a cell, a dose rate of 1mGray per year
produces 1 Actual DSB (PCC) every 185 years
1 DSB every 25 years
1 SSB per year
1 base damage every 4 months
1 LMDS every 2.5 years

Human body has 10^{14} cells, a dose rate of 1mGray per year
produces in 1 second
2.5×10^6 Actual DSB per second
1.9×10^7 DSB every second
4.8×10^8 SSB
1.4×10^9 base damage
1.9×10^8 LMDS

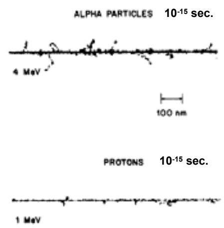
[*Abkowitz et al. Blood 100, 2665*
Number of pluripotent hematopoietic stem cells per human ~1.12×10^4 - 2.24×10^4]
? Calculate # of DSBs per dose.

J.F.Ward, 2007

Comparison of radical distribution from alphas and protons with that of electrons



J.E. Turner et al. Radiat. Res. 96, 437



Hamm et al. Radiat. Res. 104, Suppl. 8, s20.

"New" Paradigms of Radiation Action

- Apoptosis
- Bystander Effect
- Chromosome Instability
- Death Inducing Effect
- Gene Induction
- Low Dose Hypersensitivity
- Protein Mobilization

From: **The Breakdown of Desoxyribonucleic acid under Deuteron and Electron Bombardment.**

C.L. Smith Arch Biochem. Biophys. 46. 12-17

"The assumption made is plausible and perhaps not too improbable and is possibly true in essence if not in detail. It has not, however, yet been confirmed by experiment."