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Session: TU-A-BRE-3 (last number indicates order within session)
Date and Time: Tuesday July 22, 2014 from 7:30 to 9:30 am
Location: Ballroom E
Abstract #23482
Learning Objectives

- Review models and mechanisms connecting radiation biology at the molecular and cellular levels to radiation biology at the tumor and tissue level
  - Focus on effects of particle linear energy transfer (LET)
- Is the RBE for DNA damage useful for predicting cell survival?
- Is the RBE for cell survival useful for predicting the RBE for clinical endpoints?
Spatial Pattern of Energy Deposits on the Molecular and Cellular Levels ("Track Structure")

Tracks formed by ions in water (70 keV/μm)

Structure of the tracks produced by particles with the same LET are not quite the same and can produce different biological effects. However, if we “zoom out” to the macroscale (> 0.1 to 1 mm), the tracks of even very high LET particles look quite similar.

RBE effects must arise from the cellular and subcellular features of tracks – even for clinical endpoints!

Initial Damage to a Critical Molecule

Absorbed Dose

Radiation

~ 2 nm

Cluster of damaged nucleotides ("lesions") formed by passage of charge particle by DNA

Spatial pattern energy deposits determines local complexity of the cluster

Segment of a 4 MeV α particle (\(^{4}\)He\(^{2+}\))

Overall, a 1 Gy dose damages about 1 in 10\(^6\) nucleotides.
A Paradigm to Connect DNA Damage to Local Tumor Control

DNA Damage

Tumor Cell Survival

Incorrectly repaired Damage

Reproductive Death

Failure

Control

No Damage

Lethal after biological processing

Unrepairable Damage

> 1 survive

Black Lines: potential molecular and cellular pathways (mechanisms)

Black Dashed Lines: transition from cell to tissue-level biology
Reproductive Death?

*Reproductive* death is a general term that encompasses all *modes* of cell death, *including cells that remain metabolically active and intact but unable to divide*…

- *apoptosis*
- *necrosis*
- *mitotic catastrophe*

*Delayed cell death* (days or weeks later)

*Permanent or quasi-permanent (> 10-14 days)*

*Loss of reproductive potential*
Clustering of DNA lesions

Groups of several DNA lesions within one or two turns of the DNA are termed a *cluster* or *multiply damaged site* (MDS)*

- Undamaged DNA segment (20 bp)
- Organic base
- Sugar-phosphate backbone

(a) Base damage in opposed strands
(b) Complex SSB with opposed base damage
(c) Complex SSB with adjacent base damage
(d) Complex DSB

Most critical category of DNA Damage

* Clustered lesions are also referred to as *locally multiply damaged sites* (LMDS)
Are all DSB Lethal? What about SSB?

After 1 Gy dose of low LET radiation, a typical human cell sustains $45 \pm 10$ DSB Gy$^{-1}$ cell$^{-1}$ and $1000 \pm 200$ SSB Gy$^{-1}$ cell$^{-1}$. If all DSB are lethal, the fraction of cells that will survive a 2 Gy dose is

$$S = \exp(-45 \text{ DSB Gy}^{-1} \cdot 2 \text{ Gy}) \sim 10^{-40} \left(10^{-31}, 10^{-48}\right)$$

Only those cells that do not sustain a radiation-induced DSB survive (Poisson distribution of DSB among irradiated cells)

For comparisons, many published studies indicate a surviving fraction of 0.1 (repair compromised) to 0.9 (repair proficient) cells after a 2 Gy dose of radiation. Only way to reconcile observations is

- <2% of initial DSB formed in a cell are lethal
- <0.1% of initial SSB formed in a cell are lethal

Cells are really good at repairing DNA damage, even DSB!

See also the classic review: DT Goodhead. Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. IJRB 65(1): 7-17 (1994).
RBE for DSB induction

\[ \Sigma = \text{number of DSB Gy}^{-1} \text{ cell}^{-1} \]

\[ = \text{slope of line} \]

\[ D_\gamma = \text{dose of reference radiation} \]

\[ D_p = \text{dose of proton} \]

**Want:**

Number DSB = \( \Sigma_\gamma D_\gamma = \Sigma_p D_p \)

\[ RBE_{DSB} \equiv \frac{D_\gamma}{D_p} = \frac{\Sigma_p}{\Sigma_\gamma} \approx 1.5 \]

RBE is an example of an “isoeffect calculation”

Trends in $RBE_{DSB}$ with proton LET


- **Filled Red Symbols**: Track Structure Simulation (Friedland et al. 2003)

- **Lines**: Monte Carlo Damage Simulation* (MCDS)

DSB are *only* category of DNA damage that increases with increasing particle LET (*additional evidence SSB less critical form of DNA damage than DSB*)

* Semenenko and Stewart 2004, 2006, Stewart et al. 2011
Why are DSB so effective at killing cells? *(Breakage and Rejoining Theory)*

**Proximity Effects:** *pairs* of DSB formed in close spatial *and* temporal proximity are more likely to rejoin incorrectly than *pairs* of DSB separated in time and/or space (*dose rate and LET effects*)

Lethal and Non-Lethal Aberrations

Symmetric (reciprocal) translocation
Correct rejoining

Centromere

Dicentric
Acentric fragment

Start → A or B or C

Dicentrics and acentric fragments are usually lethal in the reproductive sense because segregation of chromosomes at mitosis is disturbed. In contrast, correct DSB rejoining and symmetric (reciprocal) translocations are consistent with continued cell division.

Is there a 1:1 relationship?

$S = e^{-Y}$

$S =$ fraction that survive

$Y =$ avg number of lethal aberrations per cell

AC 1522 normal human fibroblasts irradiated by x-rays

Source: Cornforth and Bedford, *Rad. Res.*, 111, p 385-405 (1987). See also Figure 3.4 in Hall (p. 37)
Linear-Quadratic (LQ) Model for Cell Survival

**Pairs** of DSB formed by
same track interact
(intra-track interactions)

\[ Y(D) = \alpha D + \beta D^2 = \alpha D \left( 1 + \frac{D}{\alpha / \beta} \right) \]

**Pairs** of DSB formed by
different tracks interact
(inter-track effect)

Cell survival after dose \( D \)

\[ S(D) = e^{-Y(D)} = e^{-\alpha D - \beta D^2} \]

Only those cells without a lethal aberration in their DNA retain the ability to divide and produce viable progeny ("reproductive survival").

Figure 3.5 in EJ Hall and AJ Giaccia, Radiobiology for the Radiologist, 6th Ed, Lippincott Williams & Wilkins (2006)
Connecting **DSB** to Local Tumor Control

Grey Dashed Lines: *low probability* molecular and cellular pathways (*mechanisms*)

**Double Strand Break (DSB)**

All or most DSB lethal

Lethal after biological processing

Black Lines: *high probability* molecular and cellular pathways (*mechanisms*)

No lethal aberrations

No DSB

≥ 1 survive

**Tumor Cell Survival**

**Chromosome Aberrations**

Reproductive Death

Are trends in the RBE for DSB induction qualitatively and quantitatively similar to the RBE for cell survival?

Black Dashed Lines: transition from cell to tissue-level biology
Low and High Dose RBE (cell survival)

RBE for a specific dose (cell survival level)

\[ RBE = \frac{D_\gamma}{D_p} \]

\[ \cong \frac{9.2 \text{ Gy}}{2.8 \text{ Gy}} = 3.3 \text{ (1% survival)} \]

Low Dose RBE: \(-\ln S \cong (\alpha D)_\gamma = (\alpha D)_p\)

low dose \(RBE_{SF} = \frac{D_\gamma}{D_p} = \frac{\alpha_p}{\alpha_\gamma}\)

“\(RBE_{\text{max}}\)"

High Dose RBE: \(-\ln S \cong (\beta D^2)_\gamma = (\beta D^2)_p\)

high dose \(RBE_{SF} = \frac{D_\gamma}{D_p} = \sqrt{\frac{\beta_p}{\beta_\gamma}}\)

“\(RBE_{\text{min}}\)"

\(\alpha D\) dominates \((D << \alpha/\beta)\)

\(\beta D^2\) dominates \((D >> \alpha/\beta)\)
Is $RBE_{DSB}$ predictive of $RBE_{SF}$?

Little if any evidence $RBE_{SF}$ ($^1H^+$ and $^4He^{2+}$) is related to $RBE_{DSB}$, or so it seems...

Measured data from Prise et al. IJRB, 58, p 261-277 (1990)

* Semenenko and Stewart 2004, 2006, Stewart et al. 2011
A Mechanistic Model for $\alpha$ and $\alpha/\beta$

The Repair-Misrepair-Rixation (RMF) model (Carlson et al. 2008) predicts, in the limit when the $D$ is small compared to $\alpha/\beta$, that

\[ \alpha = \theta \Sigma + \kappa \bar{z}_F \Sigma^2 \]
\[ \beta = \frac{\kappa}{2} \Sigma^2 \]
\[ \frac{\alpha}{\beta} = \frac{2}{\Sigma} (\theta / \kappa) + 2 \bar{z}_F \]

$\theta$, $\kappa$ are adjustable cell- or tissue-specific parameters related to biological processing of DNA damage (independent of LET and $O_2$ concentration)

$\Sigma$ is the number of DSB Gy$^{-1}$ Gbp$^{-1}$ (or per cell); estimate using the MCDS (strong function of LET and $O_2$ concentration)

$\bar{z}_F$ is the frequency-mean specific energy (in Gy) delivered to the cell nucleus (strong function of LET but independent of $O_2$ concentration) – estimate with the MCDS or other Monte Carlo code(s)

How is $RBE_{DSB}$ related to $RBE_{SF}$?

With the RMF-motivated formulas for $\alpha$ and $\beta$, the low and high dose $RBE_{SF}$ is

$$\alpha = \theta \Sigma + \kappa \bar{Z}_F \Sigma^2$$
$$\beta = \frac{\kappa}{2} \Sigma^2$$

"$RBE_{\text{min}}$" high dose $RBE_{SF} = \sqrt{\frac{\beta_p}{\beta_\gamma}} = RBE_{DSB}$

"$RBE_{\text{max}}$" low dose $RBE_{SF} = \frac{\alpha_p}{\alpha_\gamma} \cong RBE_{dsb} \left\{ 1 + RBE_{dsb} \frac{\bar{Z}_F \Sigma_\gamma}{\theta / \kappa} \right\} \geq RBE_{dsb}$

$D$ is “small” compared to $\alpha / \beta$

Intra-track DSB interactions increase with increasing LET because of proximity effects

$$\frac{\bar{Z}_F \Sigma_\gamma}{\theta / \kappa} \propto \frac{\Sigma_\gamma}{\theta / \kappa} \cdot LET$$
Is $RBE_{DSB}$ predictive of $RBE_{SF}$? Version 2.0

Reasonable fit to cell survival data for all energies.

Low dose $RBE_{SF} \geq RBE_{DSB}$

Measured data from Prise et al. IJRB, 58, p 261-277 (1990)

* Semenenko and Stewart 2004, 2006, Stewart et al. 2011
Dosimetry of Short-Range Particles is Tricky...

When the CSDA range of a charge particle is of the same order of magnitude as the dimensions of the biological target, dosimetry needs to be corrected for:

- Change in stopping power within target
- Energy and path length straggling
- Finite particle range ("stoppers"), energy and angular distribution of particles incident on target

For a monoenergetic particle incident on a 5 μm target

<table>
<thead>
<tr>
<th>Particle</th>
<th>Range (μm)</th>
<th>LET (keV/μm)</th>
<th>D/Φ (nGy-cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Reported</td>
<td>Entrance</td>
</tr>
<tr>
<td>1.9 MeV $^1$H$^+$</td>
<td>67.7</td>
<td>17.0</td>
<td>16.8</td>
</tr>
<tr>
<td>1.15 MeV $^1$H$^+$</td>
<td>29.9</td>
<td>24.0</td>
<td>24.4</td>
</tr>
<tr>
<td>0.76 MeV $^1$H$^+$</td>
<td>15.9</td>
<td>32.0</td>
<td>32.5</td>
</tr>
<tr>
<td>3.8 MeV $^4$He$^{2+}$</td>
<td>25.3</td>
<td>110.0</td>
<td>108.7</td>
</tr>
</tbody>
</table>
Fit with “Corrected” Dosimetry

Improved fit to measured data with small (quite plausible) changes in the mean particle energy (< 10 μm shift)

Measured data from Prise et al. IJRB, 58, p 261-277 (1990)
Is $RBE_{DSB}$ predictive of $RBE_{SF}$? *Version 2.1*

For protons with an $LET \leq 20 \text{ keV/μm} (\geq 2 \text{ MeV})$, RBE is about the same in cells irradiated under normoxic and anoxic conditions (no change in OER from $^{60}\text{Co γ-rays}$).
Impact of Uncertainties on “observed” RBE

RBE is ratio of doses that produce same biological effect

\[ RBE = \frac{D_\gamma \pm \sigma_\gamma}{D_p \pm \sigma_p} \]

RBE 1.1 \(\pm\) 0.1 (blue shaded region)

1.8% uncertainty in equivalent physical dose: RBE = 1.1 \(\pm\) 0.05

3.8% uncertainty in equivalent physical dose: RBE = 1.1 \(\pm\) 0.1

10% uncertainty in equivalent physical dose: RBE = 1.1 \(\pm\) 0.3
Do we just need more accurate dosimetry

and better dose-response models

(e.g., RMF model)?

in vivo studies

Need ± 3.8% accuracy in equivalent doses for RBE = 1.1 ± 0.1

Adapted from Figure 2 in Paganetti, Niemierko, Ancukiewicz, Gerweck, Goitein, Loeffler, and Suit, Relative Biological Effectiveness (RBE) Values for Proton Beam Therapy, IJROBP 53(2) 407-421 (2002).
Strong evidence for spatial (and LET) variations in proton RBE despite uncertainties ...

Low energy proton “sting” on distal edge of a pristine Bragg peak

Adapted from Figure 3 in Paganetti, Niemierko, Ancukiewicz, Gerweck, Goitein, Loeffler, and Suit, Relative Biological Effectiveness (RBE) Values for Proton Beam Therapy, IJROBP 53(2) 407-421 (2002).
RBE effects in a 163 MeV pencil beam

Tuned MCNP 6.1 model of 163.25 MeV pencil beam to match measured depth-dose profile (SCCA proton facility, Seattle, WA).

- Low Dose RBE_{SF} (α/β = 1 Gy)
- RBE due to protons slowing down below ~13 MeV (≥ 3.5 keV/μm)
- RBE ≥ 1.1
- 2 mm

* Really easy way to generate dose-averaged RBE in MCNP. See supplemental slides.
Proton RBE for Healthy Organs and Tissues?

Absorbed Dose

Radiation

10^{-18} to 10^{-10} s

Chemical Repair

10^{-3} s

O_2 fixation

Ionization Excitation

10^{-6} s

1 Gy ~ 1 in 10^6

Correct Repair

10^2 s \uparrow 10^4 s

Enzymatic Repair (BER, NER, NHEJ, …)

DNA damage

Incorrect or Incomplete Repair

Chronic hypoxia (> 1-2 h)

Non-Viable

10^3 s \downarrow 10^5 s

Loss of Function and Remodeling

10^6 s

Angiogenesis and Vasculogenesis

Inflammatory Responses

Self renewal and Differentiation

Heritable Effects

10^7 s

Germline

Genome Instability

Somatic cells

Viable

Small- and large-scale mutations (point mutations and chromosomal aberrations)

2nd Cancer

Clonal Expansion

10^8 s

Neoplastic Transformation

10^8 s

Early Effects (erythema, …)

Local Control

Late Effects (fibrosis, …)

Late Effects

10^8 s

Loss of Function and Remodeling

10^6 s

Non-Viable

10^3 s

Chronic hypoxia (> 4-10 h?)

Viable

Small- and large-scale mutations (point mutations and chromosomal aberrations)
UW Experience with Fast Neutrons

80-90% of absorbed dose to patient is from lower energy protons \( (E_{\text{avg}} \approx 16 \text{ MeV}) \)

Tolerance doses derived from over 25+ years of clinical experience

Used as a guide for tolerance doses in carbon ion therapy

What can fast neutron therapy tell us about RBE effects in a proton Bragg peak?
Neutron TD5/5 Dose \((\text{Brainstem and Lung})\)

\[(\alpha/\beta)_\gamma \approx 1.6 \text{ Gy} \]

**Neutron RBE**

\((\text{clinical endpoint})\)

\[(\alpha/\beta)_\gamma \approx 10 \text{ Gy} \]

**Blue dotted lines** RMF predicted neutron TD with \(RBE_{DSB} = 2\)

Usual caveats apply about accuracy of tolerance dose estimates
Neutron TD5/5 Dose (Cauda Equina and Cord)

\[(\alpha/\beta)_\gamma \approx 3.0 \text{ Gy} \]

\[(\alpha/\beta)_\gamma \approx 2.2 \text{ Gy} \]

- Neutron (Laramore 2007)
- UW SBRT program (2013)
- Emami et al. 1991

Number of Fractions

TD for Cauda Equina (nerve damage)

TD for Spinal Cord (myelitis necrosis)
Neutron TD5/5 Dose *(Skin and Ribs)*

- \((\alpha/\beta)_\gamma \approx 9.0 \text{ Gy}\)
- \((\alpha/\beta)_\gamma \approx 3.0 \text{ Gy}\)

- Graphs showing the TD for Skin (ulceration/necrosis) and TD for Ribs (pathological fracture) vs. number of fractions.
  - Data points and curves from Neutron (Laramore 2007), UW SBRT program (2013), and Emami et al. 1991.
Fast Neutron RBE for Selected Tissue

Filled circles: \( \text{RBE}(n = 16) = \frac{TD_\gamma}{TD_n} \)

\[ \text{Avg RBE} = 2.6 \pm 0.3 \]

27 tissues/ endpoints

**Red Dashed line:** Monte Carlo ("first principles") simulation of neutron RBE for DSB induction.

**Blue Shaded Region:** Estimate of RBE for DSB induction derived from analysis of *in vitro* cell survival data for 30 human tumor cell lines (Warenius *et al.* IJROBP 1994).

Clinical RBE \( \geq RBE_{DSB} \), as predicted by the RMF model
Summary and Conclusions

- Much of the uncertainty in proton RBE due to
  - Uncertainty in dosimetry of the reference radiation and proton beam
  - Need for mechanistic dose-response models to guide the interpretation and analysis of measured data

- $RBE_{DSB}$ (RBE_{min}) and low dose $RBE_{SF}$ (RBE_{max}) are relevant biological endpoints for (1) local tumor control and (2) tolerance doses for healthy organs and tissues

- Ample (very strong) evidence that spatial/LET variations in proton RBE are real and clinically relevant (exploitable)
  - Sticking with a constant $RBE = 1.1$ is a missed opportunity to enhance the therapeutic ratio!
Thank You!

Supplemental Slides…

- Acknowledgements
- Example of an easy way to setup dose-weighted RBE calculations in MCNP and MCNPX (*DE DF modified F6 tally*)
- Is dose-averaged LET a could surrogate for $RBE_{DSB}$ and/or the $RBE_{SF}$?
- Approximate formula linear and linear-quadratic formulas to estimate $RBE_{DSB}$ as a function of proton LET
- Why does $RBE_{DSB}$ increase with increasing LET and the RBE for SSB and base damage decrease with increasing LET?
- Why are some DSB more lethal than others?

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NOTE: “trawets” = “stewart” spelled backwards.
Acknowledgements

*Entire UW physics group* but especially D. Argento, G. Sandison, C. Bloch, E. Ford, F. Yang; other UW faculty: J. Schwartz, G. Laramore, U. Parvatheni

Example of $D \times \text{RBE}$ tally in MCNP

<table>
<thead>
<tr>
<th>FC1026</th>
<th>RBE-weighted proton (1H+) dose; DSB induction (aerobic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1026:H 3</td>
<td></td>
</tr>
<tr>
<td>FM1026 0.1602</td>
<td></td>
</tr>
<tr>
<td>DE1026 1.000E-03 2.000E-03 3.000E-03 4.000E-03 5.000E-03 6.470E-03</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>6.000E-02 7.000E-02 8.000E-02 9.000E-02 1.000E-01 2.000E-01</td>
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</tr>
<tr>
<td>3.000E-01 5.000E-01 9.000E-01 1.000E+00 1.100E+00 1.300E+00</td>
<td></td>
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<tr>
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<tr>
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<td></td>
</tr>
<tr>
<td>1.001E+00 9.995E-01</td>
<td></td>
</tr>
</tbody>
</table>

Above tally will record $D \times \text{RBE}_{\text{DSB}}$. Divide by dose (separate tally) to get dose-averaged RBE.

Analytic way to estimate an approximate $RBE_{DSB} \times \text{Dose}$ for proton beams?

Recall

$$\frac{D(x)}{\Phi(x)} = \frac{S(x)}{\rho} = \frac{LET_\infty(x)}{\rho} \quad \therefore \quad \frac{D(x)}{\Phi(x)} = \frac{LET_\infty(x)}{\rho}$$

If we know the LET and dose per unit fluence at a reference location $x_r$, LET at other locations along depth-dose curve computed from

$$LET_\infty(x) = LET_\infty(x_r) \frac{D(x)}{\Phi(x)}$$

$$RBE_{DSB}(x)D(x) = \left( mLET_\infty(x) + b \right) D(x)$$

$m = 0.03193 \ \mu\text{m/keV} \quad \text{and} \quad b = 0.98274$

Simple formulism to connect patient-specific QA measurements of dose-average LET to $RBE_{DSB}$ and (hence) the $RBE_{SF}$ (via RMF model)?
**LET** sub D instead of **RBE** sub DSB or **RBE** sub SF?**

For a clinically relevant* range of proton energies (**LET** < 25 keV/µm), dose-averaged **LET** is a good surrogate for **RBE** sub DSB and the low dose **RBE** sub SF.

\[
m = 0.03193 \frac{RBE}{(keV/\mu m)}
\]

\[
b = 0.98274
\]

For tumors and/or tissues with a low \(\alpha/\beta\), **RBE** sub SF may be larger than **RBE** sub DSB by 25-30% larger at 25 keV/µm.

* Caveat: ± 2 mm of the Bragg peak really low energy protons (< 1-5 MeV) contribute in a substantial way to dose and RBE.
LQ fit to proton $RBE_{DSB}$ as function of LET

To better capture trends in the RBE for DSB induction as a function of LET, a linear-quadratic (LQ) fit is highly recommended.

$$RBE_{DSB} = a \cdot LET^2 + b \cdot LET + c$$

$$a = 6.771 \times 10^{-3}$$
$$b = 2.553 \times 10^{-2}$$
$$c = 9.969 \times 10^{-1}$$

* Coefficients for fit may need to be adjusted slightly to correct for uncertainties in proton LET.
Ionization Density and Cluster Complexity

Secondary ionization (δ-rays)

+ 500 eV electron

Segment of a 4 MeV α particle (¹⁴He²⁺)

1.8 to 2.3 nm

Number of DNA lesions per cluster tends to increase with increasing particle LET.
Why does $RBE_{DSB} \uparrow$ and $RBE_{SSB}$ and $RBE_{Bd} \downarrow$?

A cluster categorized as a DSB cannot also be categorized as a (simple or complex) SSB or as a (simple or complex) cluster of nucleotides with base damage – mutually exclusive categories of DNA damage.

Cluster = 2 nucleotides with base damage

Cluster = complex SSB

Cluster = complex DSB

Chance a cluster will contain a pair of opposed strand breaks within about 10 bp increases (i.e., be a simple or complex DSB) as LET and the number of DNA lesions per cluster increases.
Why are some DSB (more) lethal and others not?

Answer: we don’t know for sure...

Hypotheses:

(1) Some DSB are unrepairable (unrejoinable) or more slowly rejoined than others because of the local (spatial) complexity of DNA lesions

(2) DSB formed in close spatial and temporal proximity to other DSB are more often mis-rejoined to form chromosome aberrations than DSB separated in time and/or space (breakage and reunion theory)

(3) Combination of mechanisms (1) and (2)

RMF model (Carlson et al. 2008) tends to emphasize mechanism 2
Critical MCDS and RMF Literature Citations