Distribution of chromosome breakpoints in human epithelial cells exposed to low- and high-LET radiation

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mBAND Analysis

XCyte 5-labeling scheme

DEAC (Ex 426 nm / Em 480 nm)
FITC (Ex 502 nm / Em 530 nm)
Spectrum Orange (Ex 559 nm / Em 588 nm)
Texas Red (Ex 595 nm / Em 615 nm)
Cy5 (Ex 649 nm / Em 670 nm)
Example of chromosome 3 painted with mBAND

Interchromosomal exchange (Complex)

Deletion (Ring)

Normal

Normal
Intrachromosomal exchange (inversion)

Interchromosomal exchange

Example of chromosome 3 painted with mBAND

Intrachromosomal exchange (inversion)

Interchromosomal exchange
Irradiation

High Dose Rate

$^{137}$Cs γ-ray 2.0 Gy/min University of Texas, MD Anderson Cancer Center
Fe ions 0.5 Gy/min NASA Space Radiation Laboratory / BNL

Low Dose Rate

$^{137}$Cs γ-ray 1.7 cGy/h NASA/JSC
Neutron 2.5 cGy/h Los Alamos Nuclear Science Center (LANSCE) 30L

Neutron energy spectrum on the ISS, measured spectra on Mir and the normalized LANSCE energy spectra.

The LANCE neutron energy spectrum is similar over a wide energy range to expected spectrum inside the International Space Station (ISS).

Badhwar G.D. et al. (2000)
Induction of chromosome 3 aberration in human cells by neutrons, Fe-ions or γ-rays

Relative Biological Effectiveness (RBE)

- Fe: 8.4
- Neutron: 26.4
Frequency distributions of breaks/chromosome 3

- **γ-rays (2 Gy/min)**
- **Fe-ions (0.5 Gy/min)**
- **Neutrons (2.5 cGy/h)**

The graphs show the frequency distributions of breaks/chromosome 3 for different radiation types and doses.

- **γ-rays (2 Gy/min)**: The fraction of damaged chromosome 3 is measured at 2 Gy and 4 Gy, with error bars indicating the variability.
- **Fe-ions (0.5 Gy/min)**: Doses include 0.5 Gy, 1 Gy, 1.5 Gy, and 2 Gy, with similar frequency distribution analysis.
- **Neutrons (2.5 cGy/h)**: Doses range from 0.05 Gy to 0.2 Gy, with a focus on neutron impact.

The legend at the bottom of the page indicates the color coding for different numbers of breaks: 1 break (red), 2 breaks (orange), 3 breaks (green), and ≥4 breaks (blue).
Induction of interchromosome exchanges (A) and intra-chromosome exchanges (B) in human chromosome 3 by neutrons, Fe-ions or γ-rays.

The dose responses for interchromosomal exchanges were linear in all four exposures. However, the dose response for intrachromosomal exchanges were none linear. Increasing dose of high dose rate exposure (Fe-ions or γ-rays) increase the fraction of cells with intrachromosome aberrations, whereas increasing dose of low dose rate exposure (neutrons or γ-rays) does not affect the fraction of cells with intrachromosome aberrations.
Interchromosome exchanges broken down as simple and complex types

Complex exchange: Chromosome interexchanges involving at least 3 breaks in two or more chromosomes
**Induction of inversion**

![Diagram showing induction of inversion with different dose levels.](image)

The graph shows the fraction of inversion in cells induced by different sources of radiation:

- **γ-rays (1.7 cGy/h)**: The fraction of inversion increases with dose.
- **γ-rays (2 Gy/min)**: Similar to γ-rays (1.7 cGy/h) but with a higher dose rate.
- **Fe-ions (0.5 Gy/min)**: The fraction of inversion is significantly higher compared to γ-rays.

The x-axis represents the dose in Gy, and the y-axis represents the fraction of inversion in the cell.
Classification of inversion involved aberrations in chromosome 3

- Inversion (simple)
- Inter-exchange involved Inversion
- Intra-exchange involved Inversion
- Inter-exchange and Intra exchange involved Inversion

Graph showing the fraction of total inversion for different radiation exposures:
- γ-rays 4Gy
- Fe
- Neutron

Legend:
- Inv
- Inv + Intra
- Inv + Inter
- Inv + Inter + Intra
Chromosome rearrangements in human cancer (Olopade et al.)

### Table 6.2: Nonrandom Chromosome Abnormalities in Malignant Myeloid Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome Abnormality</th>
<th>Involved Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>t(9;22)(q34;q11)</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td>CML blast</td>
<td>t(9;22)(q34;q11)</td>
<td>BCR-ABL</td>
</tr>
<tr>
<td></td>
<td>+Ph or t(17q)</td>
<td></td>
</tr>
<tr>
<td>CMMoL</td>
<td>t(15;12)(q25;p13)</td>
<td>PDGFBB-TEL</td>
</tr>
<tr>
<td>AML-M2</td>
<td>t(8;21)(q22;q22)</td>
<td>ETO-AML</td>
</tr>
<tr>
<td>APL-M3, M5V</td>
<td>t(15;17)(q22;q11-12)</td>
<td>PML-RARA</td>
</tr>
<tr>
<td>Atypical AML</td>
<td>t(11;17)(q23;q12)</td>
<td>PLZF-RARA</td>
</tr>
<tr>
<td>AMLMoL-M4E0</td>
<td>inv(16)(p13q22) or</td>
<td>MYH16-CBF2</td>
</tr>
<tr>
<td></td>
<td>t(16;16)(p13;q22)</td>
<td></td>
</tr>
<tr>
<td>AMLMoL-M4 or M5</td>
<td>t(6;11)(q27;q23)</td>
<td>AFB-MLL</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p22;q23)</td>
<td>AFB-MLL</td>
</tr>
<tr>
<td>AML-M7</td>
<td>t(12;22)(p13;q12)</td>
<td>RPN1-EVI1</td>
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<tr>
<td>AML</td>
<td>t(3;21)(q26;q26)</td>
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<tr>
<td></td>
<td>t(3;5)(q22;q34)</td>
<td>MLF1/NPMI</td>
</tr>
<tr>
<td></td>
<td>t(7;11)(q35;p15)</td>
<td>DEK-CAN (NUP214)</td>
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<tr>
<td></td>
<td>t(8;16)(p11;q13)</td>
<td>HOX9-NUP98</td>
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<tr>
<td></td>
<td>t(9;12)(q34;p13)</td>
<td>MQL-CBP</td>
</tr>
<tr>
<td></td>
<td>t(12;22)(p33;q13)</td>
<td>TEL-ABL</td>
</tr>
<tr>
<td></td>
<td>tr16;23(q11;12)</td>
<td>TEL-AML</td>
</tr>
<tr>
<td></td>
<td>del(7q)</td>
<td>TLS(FUS)-ERG</td>
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<tr>
<td></td>
<td>del(5q)</td>
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</tr>
<tr>
<td></td>
<td>del(20q)</td>
<td></td>
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<tr>
<td>Therapy-related AML</td>
<td>del(7q) and/or</td>
<td>TEL; p273(R/</td>
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<tr>
<td></td>
<td>del(5q) and/or</td>
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<td></td>
<td>del(2p) and/or</td>
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<tr>
<td></td>
<td>det(20q)</td>
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<tr>
<td></td>
<td>det(14q)</td>
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</tr>
<tr>
<td>EAP/MDS1/EVI1-AML</td>
<td>det(20q) and/or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(11;23)</td>
<td>IRF1</td>
</tr>
<tr>
<td></td>
<td>a;21(q26);q22)</td>
<td>MLL</td>
</tr>
</tbody>
</table>
Distribution of total breaks

![Graphs showing the distribution of total breaks across different bands and doses.](image)
Fragment ends participating in interchromosomal exchanges
Fragment ends participating in intrachromosomal exchanges

A

B

C

D

Fraction of total fragment ends

Band

1 3 5 7 9 11 13 15 17 19 21 23
Interchromosome exchanges

Neutron

Gamma low dose rate

Fe

Gamma high dose rate
Statistical analysis

Inter-chromosomal breaks

Intra-chromosomal breaks
intrachromosomal exchange events between two fragment ends

Low-LET

High-LET
2-D representation of the locations of different segments of Chromosome 3 inside the cell nucleus.
Comparison between the distributions of the genes and of the breakpoints
• Low- and high-LET radiations produced distinct breakpoint distributions.

• The difference of the breakpoint distributions between low- and high-LET only appeared in break ends involved in interchromosome exchanges.

• The breakpoint distributions for break ends participating in intrachromosome exchanges were similar.

• Gene-rich regions do not necessarily have more chromosome breaks.

• High-LET appeared to produce long live (data not shown) or longer live breaks that can migrate a longer distance before rejoining with other breaks.

• Domains occupied by different segments of the chromosomes may be responsible for the breakpoint distribution.
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