Radiation Carcinogenesis

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Lecture Outline

- History of radiation
- Fundamentals of radiation biology and physics
- Radiation carcinogenesis
- Radiation for cancer therapy
Radiation –
the complete process by which energy is emitted by one body, transmitted through an intervening medium or space, and absorbed by another body
Radiation History

- 1895– Roentgen discovered X-rays
- 1896– Becquerel discovered radioactivity
- 1897– Rutherford discovered α and β rays
- 1898– Curies discovered polonium and radium
- 1902– first radiation-induced cancer reported
- 1911– first report of leukemia in 5 radiation workers
1895– Roentgen
Figure 1.8  One of the very first images obtained by Röntgen using x-rays, or “Röntgen rays,” showing the bones of a hand. He took the image on December 22, 1895. (Deutsches Museum, Munich.)
1896– Becquerel

- Discovery of radioactivity
- Heard report of Roentgen’s work at the L’Academie des Sciences
- Uranium ore emitted rays capable of penetrating black paper
- Becquerel Rays ionized gases
- Did not depend on external energy source
1897– Rutherford

Physicist

Classification of α-particles (helium nuclei) and β-particles (electrons)
1898– Curies

- Marie and Pierre
- Theory of radioactivity
- Techniques for isolating radioactive isotopes
- Radiation from the atom itself: not interaction of molecules
- Discovery of radium and polonium later named radium
- First treatment of

Google celebrated her 144th birthday 11/7/11
Ionizing radiation – the ability to knock an electron from an atom

- $\alpha$ particles
  - 2 protons and 2 neutrons
  - Radon
- $\beta$ particles
  - electron equivalent
- Neutrons
- Gamma rays
- $\gamma$-rays
Non-ionizing radiation—not enough energy to ionize atoms in the material it interacts with

- Microwaves
- Visible light
- Radio waves
- TV waves
- UV radiation (except shortest wavelengths)
Units and Doses

- **Activity**
  - **Curie (Ci)**
    - # of disintegrations (decays) occurring in 1g of pure Radium per second $= 3.7 \times 10^{10}$
  - **Becquerel (Bq)**
    - 1 disintegration per second
Units and Doses

- Absorbed dose unit
  - Energy deposited per unit mass

- Roentgen (R)
  - the amount of radiation required to liberate + and - charges of one electrostatic unit of charge in 1 cm$^3$ of dry air at STP

- Roentgen equivalent man (REM)
  - Product of the absorbed dose in rads and a weighting factor, $W_R$, which accounts for the effectiveness of the radiation to cause biological damage

- RAD = unit of absorbed radiation dose
  - Currently used
Linear Energy Transfer (LET)

- Rate of energy deposition
- Loss of energy/unit distance traveled in matter
- Units = KeV/µm
- Varies depending on quality of radiation
## Linear Energy Transfer (LET)

<table>
<thead>
<tr>
<th>Particle Type</th>
<th>Linear Energy Transfer (LET)</th>
</tr>
</thead>
<tbody>
<tr>
<td>x-ray or γ-ray</td>
<td>x</td>
</tr>
<tr>
<td>β particle</td>
<td>x xxxxxx</td>
</tr>
<tr>
<td>neutron</td>
<td>x x x x x x x x x</td>
</tr>
<tr>
<td>α particle</td>
<td>xxxxxxxx</td>
</tr>
</tbody>
</table>

- The more sparsely ionizing, the more penetrating
Radiation Biology
Photoelectric Effect

Photon energy is completely absorbed by electron

- Electron leaves the orbital, leaving a hole that is filled by an electron in an outer shell
Compton Effect

Loosely bound (Free electron) – Very low binding energy
Compton Effect

Scattered Photon

Compton Electron
Pair Production

Photon passes by the nucleus’s electromagnetic field, producing a pair of electrons (e^- and e^+)
Interactions with Neutrons

Neutrons collide with a nucleus, transfers part of its energy to the nucleus, and is deflected

- Causes fast protons, $\alpha$-particles, and nuclear fragments
- $>6$ MeV

Carbon: $Z=6, A=12$
Radiation Carcinogenesis

- Radiation induced cancers arise in tissues that received radiation.
- Ionizing radiation is capable of inducing tumors in most tissues of most species at all ages.
- Exact mechanism is unknown.
- Most theories center around somatic mutations.
- No unique characteristics of radiation induced tumors.
Radiation Carcinogenesis

- All cells in the body susceptible to ionizing radiation
- Amount of damage related to the physical parameters that determine the dose received
- Radiation is a relatively weak mutagen as compared to certain chemical agents (polycyclic hydrocarbons)
- Effects are significantly modulated by secondary factors
Radiation Induced DNA Damage

- Damage to nucleotide bases
- Cross-linking
  - DNA–DNA
  - DNA–Protein
- Single-strand breaks (SSB)
- Double-strand breaks (DSB)
Studies with $^{125}$I\textsubscript{Urd}

- $^{125}$I–labeled iododeoxyuridine incorporated into cellular DNA
- $^{125}$I is an auger electron emitting radionuclide
- Each decay releases a shower of 21 low energy electrons
- Leaves behind a tellurium atom with 21 positive charges that must capture electrons to return to neutral state
Studies with $[^{125}\text{I}]\text{Urd}$

- Known to be highly cytotoxic
- Proved to induce malignant transformation
- Also highly mutagenic
- A single decay within a target gene had high probability of producing a mutation
- $[^{125}\text{I}]\text{Urd}$ proved to be much more mutagenic than x-rays
Induction of mutations by $[^{125}\text{I}]\text{Urd}$ incorporated into DNA as compared with those for several other types of radiation

Much more mutagenic than x-rays

These results suggest that the important mutagenic lesion was an incorrectly repaired DSB
Most DSBs repaired by illegitimate recombination process
  ◦ Error–prone
  ◦ Many mutagenic DNA lesions from radiation

Biologically important DNA lesion in irradiated cells appears to be the DSB

Multiple DSBs in a cell may facilitate chromosomal rearrangements
HPRT Gene Studies

- Hemizygous x-linked HPRT gene showed that radiation could induce point mutations and deletions
- Sometimes the entire gene
- Size of deletions at a hemizygous locus that can give rise to a viable cell is limited
- When both gene copies present, large scale events involving loss of heterozygosity (LOH) were the most frequent
LOH extends to include other genes on the chromosome

Proximal and distal to the target gene

LOH from a simple deletion or recombinational process

Initiating event in radiation carcinogenesis may be inactivation of a tumor suppressor gene by LOH rather than activation of a proto-oncogene such as RAS
Molecular Structure of HPRT

Point mutations predominate
Chromosome Effects

- Radiation damage to chromosomes causes breakage with two or more fragments and broken ends
  - Two broken ends can join together
    - With its “other half”
    - Nonhomologous end joining
      - Recombination of broken ends causes structural or sequence changes
Acentric & Dicentric Chromosome
Ring Chromosome
Translocation, Deletion, and
Other Cellular Constituents

- Chain breaks in carbohydrates
- Structure changes in protein
- Alterations in enzyme activity
- Changes in lipids
- Alteration in the permeability of the cell membrane
  - Affects transport
  - Affects membrane bound organelles
- Not shown significant enough for cell death
Radiation–induced Genomic Instability

- Open circles = normal wt cells
- Closed circles = mutated cells

A: most cells retain normal phenotype
B: All cells mutated by irradiation; transmitted all progeny
C and D: Irradiated cell and immediate progeny are normal and immediate progeny are not elevated
Genomic Instability

- Damage introduced to the cell by traversal of the nucleus by ionizing radiation
  - Mutation passed to all progeny

- Many damaging effects are introduced in cells that were not hit directly by radiation
Mutational event in initiation of radiation carcinogenesis most likely involves LOH of a tumor suppressor gene.

- RB tumor suppressor gene on 13q14

- Hypersensitivity of retinoblastoma patients to the induction of secondary cancers
  - Osteosarcomas in the irradiated field
Oncogenes and Tumor Suppressor

- Knockout mice heterozygous for p53 tumor suppressor gene more susceptible to radiation induced tumors

- Expression of p53 mutations occur late in radiation-induced malignant transformation

- Activation of oncogene RAS family reported in mouse lymphomas
Radiation may induce papillary thyroid carcinomas in children as a result of ret oncogene activation.

Amplification/overexpression of MDM2 found in X-ray transformed foci
- Others express mutant p53

May be multiple pathways for transformation.
Genetic alterations can occur in cells that receive no direct radiation exposure

Damage signals transmitted from neighboring irradiated cells
Bystander Effect

Timeline | Key events in the study of radiation-induced bystander effects

- First report of ‘clastogenic factors’ in the blood of exposed individuals\(^{(10)}\).
- Sister chromatid exchanges shown to occur in more cells than could have received an \(\alpha\)-particle hit\(^{(9)}\).
- Since 1997, over 250 papers have been published that describe radiation-induced bystander effects.

- 1954
- 1968
- 1992
- 1997
- 2003

- Reports of persistant genetic damage in the blood of patients given radiotherapy\(^{(11,12)}\).
- Low dose, low linear energy transfer exposure caused a medium borne cytotoxic factor to be produced\(^{(7)}\).

This Timeline shows how radiation-induced bystander effects were documented in the literature as early as 1954, but were not integrated into mainstream radiobiological studies until over 40 years later.

www.nature.com/reviews/cancer
Bystander effect in confluent cultures of normal human diploid fibroblasts, as examined by in situ immunofluorescence detection of p21waf1 by a secondary antibody conjugated to FITC. The panel on the left represents control, non-irradiated cultures, whereas the two panels on the right are from cultures irradiated with a 0.3 cGy. Focal areas were observed in which up to 50% of the cells showed enhanced expression of p21, whereas only 1-2% of the nuclei were actually traversed by an α-particle.
Bystander Effect

Figure 2 | Key aspects of radiation-induced bystander responses. Typical dose response curves for direct (a) and bystander (b) responses are shown, highlighting the commonly observed saturation of response for bystander effects.
Ultraviolet Radiation

- Nonionizing

- Limited penetration
  - Results in skin cancer

- UVA (wavelength > 320 nm)
- UVB (wavelength 290 to 320 nm)
- UVC (wavelength 200 to 290 nm)
UV Carcinogenesis

- Pyrimidine dimers
  - T–T or C–C
  - Can be repaired by nucleotide excision repair
  - Failure to repair pyrimidine dimers results in C–to–T or T–to–C transitions that give rise to missense mutations
UV Carcinogenesis

- UV-induced tumors with C-to-T point mutations in p53
- UV induced p53 mutations lead to genomic instability
  - LOH

- Xeroderma pigmentosum
  - Deficiency in nucleotide
Radiation Induced Malignancy

- Major radiation induced cancers:
  - Breast
  - Thyroid
  - Lung
  - Leukemia
Radiation Induced Malignancy–

- Japanese A-bomb survivors
- Medically irradiated patients for both benign and malignant diseases
- Medically internally administered radioactive materials
- Early radiologists and radiotherapists
Stochastic Effects

- Probability of effect increases with dose.
- Severity is not dependent on dose.
- Incidence dependent on LET.
- High doses result in cell death.
Leukemia

- Increased incidence in A-bomb survivors
  - Relative risk (RR) = 2.8
- Latent period: minimum 2–4 years, avg = 10 years
- Early radiologists and radiotherapists
  - 1929–1943: RR = 10.3
  - 1948–1963: RR = 4.1
  - Currently: RR = 1
Thyroid

- 1940’s–50’s infants treated for thymus enlargement
- Doses up to 5 Gy (500 rads) to head and neck
- Ann Arbor series
  - 20–30 rads to thyroid developed nodules and cancer 20 years later
- Latency is 5–10 year minimum with 20 year average
- Radiation induced thyroid cancer is mostly papillary and follicular
Radium watch dial painters (1920’s–30’s)
“glow in the dark” dials painted with radioluminescent paint of zinc sulfide and radium salts
Small paint brush became flattened and women “pointed” with their tongues
Ingested small quantity of radium each time
$\alpha$–particle emitter chemically similar to calcium (bone seeker)
“The Radium Girls”
Breast

- Early treatment of tuberculosis by fluoroscopic guided pneumothorax
  - RR = 10

- Patients with acute post-partum mastitis
  - RR = 4

- Atomic bomb survivors
  - RR = 4

- Breast tissue more sensitive to radiation carcinogenesis during cell proliferation (pregnancy)
Lung

- Hiroshima and Nagasaki
- Uranium miners
  - RR = 8.0
- Miner + smoking
  - RR = 20.0
Summary

www.nature.com/reviews/cancer
Radiation Therapy for Cancer

- Law of Bergonié and Tribondeau
  - Radiation is most effective on highly proliferating cells
  - Tumor cells are more susceptible to radiation-induced toxicity than normal tissue
Cell survival curves

- Shoulder of curve is the ability of a cell to accumulate damage – sublethal dose
Quality of radiation

- Loose shoulder with increasing LET
- Low LET works by indirect effect
Oxygen Enhancement Ratio
-Low LET

- Oxygen is the most potent biological radiosensitizer
  - $O_2$ will propagate free radical production
  - $O_2$ will end up bound to DNA, fixes damage

- Center of tumors is hypoxic
  - Low oxygen $\rightarrow$ Low radioresistance
Dose Fractionation

- Allows for minimal damage to normal tissue
- Allows for reoxygenation of hypoxic tumor core
- Composite survival curve
2D Radiation Therapy

Slide compliments of Dr. Anurag Singh
3D Radiation Therapy

Slide compliments of Dr. Anurag Singh
Thank you

- Questions?