Developments in radiobiology

- Developments in biology are increasing our understanding of the complex molecular pathways that control cellular processes
- Our understanding of radiation effects on cells has changed considerably over the past 10 years
- Radiobiology is exploiting these developments to find novel molecular targets for successful chemoradiotherapy approaches

Talk outline

- The rationale behind and the increasing use of concurrent chemoradiotherapy
- The importance of cell signalling and changes in our understanding of how radiation interacts with cells
- EGFR as an example of a novel target
- The concepts of redundancy and synthetic lethality and the many possible targets for novel biomarker and drug discovery

Molecularly targeted chemotherapy to improve therapeutic ratio

- The rationale behind combined modality therapy is to improve the therapeutic ratio
- There is increasing use of concomitant chemotherapy with radiotherapy
- Randomised trials provide evidence of improvements in local control and survival
- Developments in radiobiology are highlighting molecular targets for novel chemoradiotherapy approaches
Biological basis for concurrent chemoradiotherapy

- Chemotherapy may be given neo-adjuvantly, concurrently or adjuvantly
- Used concurrently:
  - Advantage: neither modality is delayed
  - Disadvantage: risk of increased toxicity
- Biological basis
  - Spatial co-operation: radiotherapy targets local and chemotherapy distant disease
  - Additive independent cell kill with no overlapping toxicity
  - Preferential sensitisation of tumour vs normal cells (or protection of normal vs tumour cells)

Meta-analysis of head & neck cancer trials involving concurrent chemotherapy

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We sometimes have a one dimensional view of a cell

Looking at cells in detail......

......highlights increasing complexity

- Aberrant cell signalling processes result in increased survival, proliferation and migration of cancer cells
A network level view of signalling is emerging

Changes in our understanding of how radiation interacts with cells

- Old paradigm: DNA is the critical macromolecule in a cell; radiation interacts with DNA leading to multiple types of damage but it is unrepaired DNA double strand breaks that cause lethality
- New paradigms: non-targeted effects occur – extranuclear and extracellular effects are also involved

Non-targeted effects

- Inducible/adaptive responses
  - A response to irradiation that is modified by a small dose of radiation given shortly before
  - Gene activation following low doses of radiation
  - Genes involved in proliferation, repair and cell kill
- Genomic instability
  - Cells that survive radiation exposure have a persistently raised level of chromosomal aberrations
  - Radiation can lead to long-lasting sub-lethal effects
- Bystander effects
  - Radiation effects can be seen on adjacent unirradiated cells
- There is evidence that cell signalling processes are involved

Are low doses harmful?

Nearly 20 people line the benches of the Merry Widow radon mine near Basin, Mont., June 10, 2004, for a midday treatment.

“Each summer, hundreds of people come to the radon health mines to relax and soak up the therapeutic aura, swearing by the healing effects of the radon gases.”

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EGFR – epidermal growth factor receptor

- Transmitting extracellular information is crucial for cell growth, movement and survival
  - Growth factor binding to cell surface receptors stimulates signalling networks
  - EGFR / erbB-1 / Her is part of a receptor tyrosine kinase family, known as EGFR, erbB or Her
  - EGFR is crucial for normal tissue development and homeostasis, null mice survive only a few days
The EGFR (ErbB/Her) family and ligands

The HER signaling network

Most cells have 20,000-200,000 EGFRs; on tumour cells the number can rise to several million

Tumour EGFR expression is associated with a poor outcome following radiotherapy
In the CHART head & neck cancer trial, high tumour EGFR expression was associated with a benefit from accelerated radiotherapy.

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**EGFR and accelerated radiotherapy**

- In the DAHANCA 6 and 7 trials, head and neck cancer patients with EGFR positive tumours responded better to moderately accelerated radiotherapy than those with low EGFR.
  - Erikson et al 2005; Radiother Oncol 74: 93-100
- EGFR antagonists are cytostatic and lead to G1 arrest, which could prevent accelerated repopulation.
- Radiopotentiating effect of the anti-EGFR drug ZD1839 was greater with fractionated than single dose irradiation suggesting it exerts an anti-proliferative effect and prevents accelerated repopulation.
  - Williams et al 2002; Br J Cancer 86: 1157-1161

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**Inverse relationship between EGFR expression and radiocurability**

- The higher the value the more dose required to cure experimental tumours.

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**Anti-EGFR strategies**

- MAbs (monoclonal antibodies)
- TKIs (tyrosine kinase inhibitors)
- Toxin conjugates
- Antisense

MAbs, monoclonal antibodies; TKIs, tyrosine kinase inhibitors.

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**Studies in experimental tumours show that anti-EGFR strategies enhance tumour response to radiation**

- Radiation stimulates EGFR signalling.
- Anti-EGFR blocks EGFR import into the nucleus, radiation-induced activation of DNA-PK and DNA repair, and increases radiosensitivity.

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**Post irradiation nuclear location of EGFR**

- Radiation stimulates EGFR signalling.
- Anti-EGFR blocks EGFR import into the nucleus, radiation-induced activation of DNA-PK and DNA repair, and increases radiosensitivity.
The rapidly expanding number of novel drugs targeting receptor tyrosine kinases

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- Systems biology is a developing field
- Interaction maps are developing
- Features of systems are modularity, buffering and functional redundancy, which aim to increase robustness
- Given the inherent complexity of and cross-talk between signalling pathways, there is considerable redundancy. This redundancy is an important part of tumour heterogeneity.
- The goal is to exploit knowledge of cell signalling pathways as system for novel drug discovery to identify inhibitors of nodal proteins
- The goal is also to identify biomarkers of response so that treatment is targeted towards tumours likely to respond
Synthetic lethality

- Systems biology argues that evolvable systems are robust against common perturbations (single-agent therapy) but fragile to simultaneous perturbations (combination therapy) – a rare event for evolution-trained networks. Fragility derives from reliance on hubs.
- Synthetic lethality: two gene are synthetically lethal if a mutation in either is not lethal but mutations in both are
- Eg, there is evidence that the anti-EGFR monoclonal antibody cetuximab is more effective towards tumours with wildtype KRAS
- This is increasing personalised medicine

Summary

- Use of concurrent chemoradiotherapy is expanding
- Most traditional cancer drugs target mitosis, DNA synthesis and DNA repair
- New molecularly targeted drugs are emerging that inhibit signalling pathways crucial for cell growth
- Signalling pathways are being studied in the context of systems biology: they are emerging as important mediators in cellular responses to radiation
- There has been a rapid increase in the number of new agents being investigated with radiotherapy in early phase trials
- The challenge is to find which drug is appropriate for which tumour/patient – involves parallel biomarker and drug discovery

Implications for radiotherapy

- Combined modality treatments will increase
- Treatment heterogeneity (personalisation) will increase
- In principle it is possible to use data from randomised trials to calculate the contribution of chemotherapy to overall tumour cell kill. The chemotherapy dose could be expressed in terms of the equivalent biologically effective dose (BED) of radiation.
- Moving towards construction of a complex tumour therapy computer programme?

The revigator

- "More illness is caused by improper water than any other reason and largely because radioactivity is lost from our daily supply of drinking water."