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DNA-dsb Repair In Prostate Cancer: New Targets and New Therapies  

Precision-Guided Radiotherapy to Kill Cancer Cells and Protect Normal Cells  

PMH Precision-Guided Radiotherapy  

- Radiotherapy involves the use of high powered X-rays to kill cancer cells by damaging their DNA and limiting their ability to reproduce  
  - cancer cells have a decreased ability to repair the DNA damage when compared to normal cells  
- New techniques are being developed in an attempt to lessen the damage to surrounding tissue  
  - such as 3-dimensional conformal radiation therapy (3-D CRT)  
- Intensity modulated radiation therapy (IMRT) is even more precise  
  - uses many very small beams and the intensity of each can be precisely controlled to 'bend' around healthy tissue.  
  
OK ! Great !  
Now add Biological Precision !!  

Theragnostics: Predict and Change Treatment  

CFIs 1 & 2: Tracking In Situ DNA Damage Signaling/Repair Complexes under Hypoxia
Sensors and Mediators

Signal Transducers & Effectors

DNA Breaks: A Way To Kill Cancer Cells

DNA-dsb Repair Pathways

Signal Transduction & DNA Repair

- EGFR inhibitors (Cetuximab) lead to decreased levels of DNA-PKcs and RAD51 and lead to elevated residual DNA-dsbs
- Radioresistant cells that over-express the RAS oncogene have elevated levels of Ku80 and DNA-dsb repair
  - Effects of Farnesyl Transferase Inhibitors on this finding?
- HDAC inhibitors (TSA, SAHA, MS-275) decrease RAD51 expression and lead to increased residual DNA-dsbs
- IGF1-R inhibitors decrease to altered HR and NHEJ
- Gemcitabine+DDP + XRT decreased repair of DNA-dsbs
- ATM, DNA-PK, PARP inhibitors lead to increased DNA-dsbs
DNA Repair and Cancer Therapy: Key Questions

- Is the level of DNA-dsb repair gene expression different in normal and malignant cells?
- If so, is there a rationale for targeting DNA repair as a new strategy?
- How could we track DNA repair in malignant and normal cells following the use of novel agents?

THE BIG PICTURE

Hypoxia → Local Control
DNA Repair ?

Increased Genetic Instability
Tumour Progression
Metastasis

Hypoxia in Cancer and BPH

Pimonidazole uptake in 92% of tumors, and in BPH in 95% of patients

Carnell, 2006
HYPOXIA Decreases HR-related Proteins In Proliferating Cells: HIF-1α/Cell Cycle Phase Independent

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Biologic and Clinical Implications

DNA Repair and Cancer Therapy: Key Questions

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Targeting HR vs NHEJ

- Use Gemcitabine or MMC with RT
  - Clinical data in bladder, lung, gynecologic and gastrointestinal cancers
- Use anti-ABL therapies (Gleevec) to reduce RAD51 levels
  - Tofilon, 2003-radiosensitized glioma cells
- Use siRNA or antisense or small molecule inhibitors to directly reduce HR (through ATM, p53, IGF1-R) or RAD51 levels
  - Numerous studies showing SER 1.2-1.5
- Target BRCA1/2 using DNA replication inhibitors
  - PARP inhibitors selectively target tumours lacking HR, but not normal cells (Ashworth, 2005)
- RT Alone: Hypoxic cell radioresistance?
  - OER of HR-mutants only 1.1-1.5 (i.e., not 2.5-3; Begg)

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Cancer Cells Deficient in HR: Toxicity to IR and CHEMO

HR/NHEJ DNA Repair Inhibition

Key Questions For DNA Repair Program

- Prostate cancers may have decreased repair ability due to altered protein expression and hypoxia: chemoprevention and treatment
  - HR vs NHEJ Inhibitors vs signaling inhibitors (EGFR, FTI, HDAC, GLEEVEC)
  - Multiple targets needed: checkpoint inhibitors + DNA repair inhibitors?
- How does hypoxia alter DNA-dsb repair?
  - Drug development issues
  - Tracking: co-staining with hypoxia and DNA repair biomarkers
- How do we track whether new drugs are working?
  - Can use invasive biopsies, non-invasive tracking of protein phosphorylation?
  - Protein-protein interactions (residual foci) may be key
- Effects on normal tissues and therapeutic ratio?
  - Very few data on normal tissues effects; prevent second malignancies?
  - SNP studies in prostate/breast just a beginning...
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