p53 - the gene that stops cancer

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Cancers - accumulation of mutations

Brake (Tumour suppressors)

Accelerator (oncogenes)
What causes mutations?

Chemicals
Radiation
Viruses
Replication errors
Multistage carcinogenesis

Normal

Increasing Mutations

Cancer
p53 turns on genes to protect cells
p53 is mutated in the DNA binding domain of many cancers
Mutant p53 contributes to cancer progression

- Loss of function

- Gain of function – actively promotes cancer
Mutant p53 contributes to cancer progression

Roth et al. (2015) *Oncogene* under review
Mutant p53 promotes organ invasion (T cell Lymphoma)

Roth et al (2015) Oncogene under review
Cancers are continually evolving (heterogeneous)
On/off gene switches are disrupted in cancer

<table>
<thead>
<tr>
<th>Genes</th>
<th>Normal tissue</th>
<th>Malignant tissue</th>
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<td>1 2 3 4 5 6 7 8</td>
<td>1 2 3 4 5 6 7 8</td>
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- **GENE ON**
- **GENE OFF**
p53 activity is a biomarker for good prognosis
YB-1 level is a biomarker for poor prognosis

Lasham et al 2012, Journal of the National Cancer Institute 104, 133-146
Y-box binding protein YB-1 inhibits p53 functions

The Y-box-binding Protein, YB1, Is a Potential Negative Regulator of the p53 Tumor Suppressor

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Elevated YB-1 may promote cancer progression

Breast cancer

- Low YB-1
  - High p53
- High YB-1
  - Low p53

Melanoma

- Low YB-1
- High YB-1

Lasham et al 2012, JNCI (breast); Cris Print (melanoma)
Inhibiting YB-1 prevents cancer in vivo

Lasham et al 2012, JNCI 104, 133-146.
p53 is important

- p53 mutant animals die of cancers
- Li-Fraumeni Syndrome
- Tumours have p53 mutations (predictive value)
- Can “re-awaken” p53 as a therapy
p53 – the gene that stops cancer

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