Extension materials for lecture 2 : Hallmarks of Cancer

About Hanahan & Weinberg

- Doug Hanahan is a physicist by background! Whilst at MIT he went to a life changing lecture on DNA by a geneticist called Salvatore Luria and he was hooked!
- Robert Weinberg discovered Ras – the first human oncogene, so he was reasonably qualified to write this overview!

Growth self-sufficiency

Growth self-sufficiency might be achieved in a variety of ways:

- Increased productions of extracellular growth signals, forming an autocrine loop e.g. Glioblastoma cells producing PDGF, or sarcoma cells producing TGF-α
- Increase trans-membrane signalling of growth signals by overexpressing the receptor : e.g. HER2/neu overexpression in breast cancer.
- Mutation of the receptor so that it is always on (e.g. BCR/Abl)
- Disrupt intracellular pathways that translate signal into gene expression changes : e.g. MAP Kinase pathway

Evading growth suppression

- Recall that tumour suppressor genes are usually normally functioning genes that encode some inhibitory feedback mechanism on cell growth.
- **Loss of function** mutations of tumour suppressor genes will lead to increased cell proliferation. A cell therefore needs to knock out both working copies of its tumour suppressor gene before cell proliferation occurs. This is the basis of the Knudsen hypothesis – It was observed in cases of retinoblastoma that some cases were familial and some were sporadic. Familial cases were younger than sporadic cases. In the familial cases, one loss of function mutation is inherited, and the other occurs in the cancer cell. In the sporadic cases, two loss of function mutations have to occur in the same cell, so it takes longer statistically for this to happen.
- Growth suppressors can block proliferation by forcing cells out of the cell cycle into the G0 state, or holding cells in a post-mitotic state
- Rb protein is also important in viral carcinogenesis. Viral oncoproteins (e.g. E6 and E7 in HPV driven cancers) sequester Rb protein and stop it from working in tumour cells.

Evading apoptosis

- Apoptosis is dependent on the function of several surface ligand receptors to initiate the downstream signalling mechanisms, such as
  - IGF and IGF1
  - FAS and FAS ligand
  - TNF alpha and TMF-R1

- Different tumours will devise different methods to inactivate p53, but in each case the end result is that the tumour cells gain the capacity to evade apoptosis.

Mechanism of inactivating p53	Typical tumours	Effect of inactivation
Amino-acid-changing mutation in the DNA-binding domain	Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus and many others	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes
Deletion of the carboxy-terminal domain	Occasional tumours at many different sites	Prevents the formation of tetramers of p53
Multiplication of the MDM2 gene in the genome	Sarcomas, brain	Extra MDM2 stimulates the degradation of p53
Viral infection	Cervix, liver, lymphomas	Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation
Deletion of the $p14^{ARF}$ gene	Breast, brain, lung and others, expecially when p53 itself is not mutated	Failure to inhibit MDM2 and keep p53 degradation under control
Mislocalization of p53 to the cytoplasm, outside the nucleus	Breast, neuroblastomas	Lack of p53 function (p53 functions only in the nucleus)

- We might be able to fight back directly against these cancer cells evasion of apoptosis. Tenovins are a recently discovered family of chemicals which may functionally bypass defective p53 and activate apoptosis. They work by blocking sirtuins, which are themselves histone deacetylases. Some promising results have been obtained in chronic myeloid leukaemia.

Replicative Immortality

- Telomerases contain reverse transcriptase enzymes (TERT), and an RNA fragment with the pattern 'CCCAAUCCC' which acts as the template for telomere elongation.
- Without telomerases, a cell dividing will manage 50-70 cell divisions before it runs out of telomere padding (the Hayflick limit). At this point it goes into reproductive senescence.
- Mutations in the telomerase gene promoter sequences are found in certain tumour types (gliomas, melanoma and hepatocellular carcinoma), and associated with a poorer outcome in patients.
- Mammals have low telomerase levels and tend to have a short growth phase. Some fish, like rainbow trout and koi carp, have high telomerase activity which allows them to continue growing throughout their lives.

Sustained angiogenesis

- Angiogenesis in normal tissue is a balance of positive and negative signalling. During wound repair, for example, angiogenesis will be promoted locally until cell growth proliferation is halted, like contact inhibition at an epithelial surface.
- Tumour angiogenesis is highly disordered and friable when compared to angiogenesis in normal tissue growth and repair
- It is interesting to note that most tumours will overexpress pro-angiogenic factors. In contrast, there are no tumours that work through the inhibition of anti-angiogenic factors.

- Angiogenesis inhibition is the putative mechanism of Avastin (bevacizumab), a monoclonal antibody that binds to the VEGF receptor and prevents binding of VEGF.

Genomic instability

- This is a very large field of study in itself. In hereditary cancers, genomic instability results from mutations in DNA repair genes and drives cancer development.
- In sporadic cancers the molecular basis of genomic instability remains unclear, but recent high-throughput sequencing studies suggest that mutations in DNA repair genes are infrequent before chemotherapy and radiotherapy.
- It is thought now that the common oncogenes found in sporadic cancers drive cell proliferation very hard. This places stress on DNA replication and mistakes occur resulting in double strand DNA breaks. When these replication errors occur in the key genome regulation pathways (TP53 and ATM) there is a marked increase in the cell's genomic instability.
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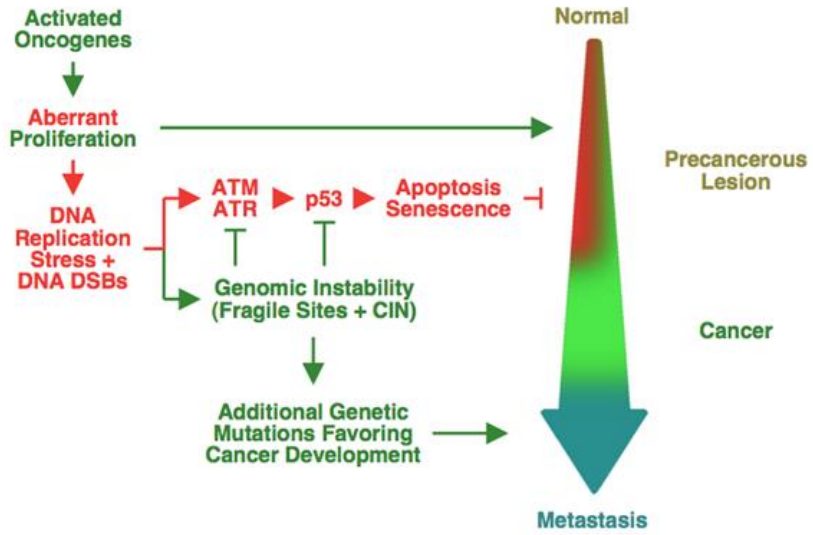

Metabolomics

- Tumour cells will often need to extract energy in conditions of low oxygen and pH. This is unfavourable for xxidative phosphorylation, but glycolysis can still be used.
- P53 mutations, and tumour hypoxia factors (HIF-1) drive glycolysis
- Tumours upregulate glucose transporters (Glut-1) to fuel glycolysis.
- Mechanisms to scavenge extra energy from glycolysis products will give tumour cells an energy advantage for growth.
- Isocitrate dehydrogenase is (IDH-1) mutated in glioma cell lines. IDH1 converts citrate into alpha ketoglutarate, releasing NADPH. It is an interesting gain of function mutation that provides tumour cells with additional energy. IDH-1 mutations in gliomas are actually associated with a better prognosis, which seems counter-intuitive given that the cells have an energy advantage for growth!

Tumour promoting inflammation

- This is a very complex field. The presence of tumour in a normal tissue environment can induce an inflammatory reaction from neighbouring cells. We see this often in the case of brain metastases for example.
- The inflammatory response may induce tumour promoting and tumour suppressing leucocytes
- Some of the cytokines released by these cells will help promote angiogenesis, and degradation of the extracellular matrix
- Some tumours may also reprogram adjacent fibroblasts whose pro-inflammatory actions help tumour infiltration and metastasis