(Oncogenic) signaling networks and signal transduction

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Clinical and Molecular Oncology
- Regulation of the normal cell cycle
- Cell cycle checkpoints
- Oncogenes are activated by different mechanisms
- Tumor suppressor genes are inactivated by different mechanisms
- Loss of heterozygosity can be achieved by multiple mechanisms
- Oncogenic events cooperate to drive tumorigenesis
Malignant transformation
The eukaryotic cell cycle is subdivided into distinct phases

prophase, metaphase, anaphase, telophase
Cell cycle progression has to be strictly regulated.
The mammalian cell cycle is driven by cyclin-dependent kinases (CDKs).
Mammalian cells are responsive to growth signals only during the $G_1$ phase.
Numerous pro-proliferative pathways converge on cyclin D synthesis.
The molecular trigger for S-phase entry - the R(estricition) point
Once the R-point is breached, cells are independent of extracellular growth signals.
Mammalian cells have evolved checkpoints to prevent cell cycle progression in case of danger after passing through the R-point.
Checkpoint activation leads to CDK inhibition
p53 is a major component of the checkpoint machinery

ATM/p53

DSB

ATM

Chk2

p53

Noxa

Puma

DSB apoptosis

Döhner et al.; NEJM, 2000
Excessive CDK4/6 activity, loss of RB1 or E2F hyper-activation induces a fail-safe mechanism.
Take home message #1:

The eukaryotic cell cycle is organized in distinct phases and progression through the cycle is driven by CDKs.
Cancer is a genetic disease
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What are the genetic events that ultimately lead to malignant transformation?
Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure.

Mutations can structurally damage gene products.
Ras is a small G-protein
Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure.
Ras is an extremely potent oncogene that controls numerous downstream pathways.
Through activating PI3K, Ras initiates AKT signaling
Take home message #2:
Proto-oncogenes can be turned into oncogenes through point mutations
Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure.

Amplifications can lead to increased gene dosage of proto-oncogenes.
Take home message #3: Proto-oncogenes can be turned into oncogenes through amplifications.
Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure.

Translocations can structurally damage gene products.
Proto-oncogenes can be activated by genetic changes affecting either protein expression or structure.

Translocations can structurally damage gene products.
The BCR-ABL fusion is the key driver of CML
Imatinib is a potent inhibitor of (BCR-)ABL
Imatinib is superior compared to IFNa/Ara-C in the first line.
Take home message #4:

Proto-oncogenes can be turned into oncogenes through translocations
Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure.

Point mutations can structurally damage gene products.
p53 is a potent tumor suppressor gene
p53 is a potent tumor suppressor gene
p53 acts as a transcription factor
Oncogenic p53 mutations frequently inactivate the DNA binding domain.
Ras can be inactivated by GTPase-activating proteins (GAPs)
NF1 is a RAS GAP that is frequently mutated in cancer
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PTEN is a phosphatase that counteracts PI3K-mediated AKT activation.
Take home message #5:

Tumor suppressor genes can be inactivated by point mutations.
Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure. (micro) deletions can lead to inactivation of TSGs.
Take home message #6:

Tumor suppressor genes can be inactivated (micro) deletions
Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure.
Tumor suppressor genes can be inactivated by genetic changes affecting either protein expression or structure.

Promoter hypermethylation can lead to inactivation of TSGs.
Take home message #7:

Tumor suppressor genes can be inactivated promoter hypermethylation
Unlike in proto-oncogenes, the second allele of a tumor suppressor gene typically has to be inactivated to drive tumorigenesis.
Rb1 and the Knudson hypothesis

- Familial retinoblastoma
- Genotype of fertilized egg
- Sporadic retinoblastoma

First somatic mutation:
- Mutant Rb allele
- Two mutant Rb gene copies

Second somatic mutation:
- Mutant Rb allele
- Two mutant Rb gene copies

Bilateral disease

Unilateral disease
Loss of heterozygosity can be achieved through mitotic recombination

Mitotic recombination can lead to loss of heterozygosity (LOH)
Loss of heterozygosity can be achieved through gene conversion.

Gene conversion can lead to LOH.
Loss of heterozygosity can be achieved through mitotic non-disjunction

Mitotic non-disjunction can lead to LOH
Take home message #8:

Loss of heterozygosity can be achieved through mitotic cross-overs, mitotic non-disjunction or gene conversion.
Pathway review
Summary

- Progression through the cell cycle is driven by CDKs

- G1 cells are responsive to mitogenic stimuli

- Oncogenic stress triggers the activation of checkpoints

- Cancer-associated mutations frequently impair the cell cycle-regulating machinery

- Oncogenes:
  - Ras, PI3K, AKT, MYC, BCR-ABL

- Tumor suppressor genes:
  - p53, p16, p14ARF, NF1, PTEN, RB1
Tumorevolution can be visualised by histology
The genetic evolution of colorectal carcinomas

1) Adenoma
2) Carcinoma in situ
3) Invasive carcinoma
4) Metastasis
Oncogenes cooperate

Diagram:
- Cloned genes injected into fertilized mouse eggs
- Some embryos yield mice carrying transgene in all their cells, including gametes
- Breed with one another

Graph:
- Tumor-free female mice (%)
- Age in days
- myc: T50 = 325 days
- ras: T50 = 168 days
- myc + ras: T50 = 46 days
Take home message #9:

Human neoplastic diseases are the result of a process called “multi-step-tumorigenesis.”
The biology of EGFR signaling

[Diagram showing the EGFR signaling pathway with key components and interactions like ligand-induced dimerization, kinase domain activation, phosphorylation sites, and downstream signaling molecules.]
(A) Plasma membrane

TK

Grb2

SH2

SH3

Sos (GEF)

Ras

GDP

GTP

downstream signaling

TK

Ras

GDP

GTP

NF1

PKC
The SRC gene encodes for an oncogenic tyrosine kinase