

## Vesalius SCALpel™ : Oncology principles

### genetics

hereditary/germ line mutation

present in gamete(s) at conception, therefore in every cell in body  
factor in 5-10% of cancers

acquired/somatic mutation

starts in one cell, present in offspring of that cell/tumor  
many cancers have multiple mutated genes acting

two main classes of tumor-producing mutations: oncogenes, tumor suppressor genes

oncogenes

proto-oncogenes are the normal genes that control cell division

mutation of proto-oncogene that leaves it permanently turned on makes it an oncogene

may also be multiple copies of a gene (amplification) that results in more product

100 recognized oncogenes, 5 classes/mechanisms of action, mutated genes produce:

1 growth factors: stimulate cell growth

overproduction of platelet derived growth factor (PDGF) promotes cell growth

2 growth factor receptors (GFR)

activated by growth factors

amplification results in too many GFR molecules making cell overly sensitive  
to growth factors

examples: EGFR/erbB and B2 (HER2/neu) gene amplification

HER2/neu present in 1/3 of breast cancers

3 signal transducers: act between GFR and nucleus

eg: abl in CML, ras in many cancers

4 transcription factors: final molecule to trigger DNA to divide

control which genes active producing RNA and protein

eg. myc: lung, leukemia, lymphoma and others

5 programmed cell death regulators

prevent cell suicide when there is an abnormality

overactivity allows bad mutations to persist

eg. bcl-2 in lymphoma

tumor suppressor genes

normal tumor suppressor genes slow cell division, repair DNA, tell cell when to die

mutation causing failure of normal function, allows cells to grow out of control

mutation of both alleles necessary (v oncogenes)

mutations both inherited and acquired

30 known tumor suppressor genes, three classes/mechanisms of action

1. genes that act on cell division

eg. RB1 (retinoblastoma)

heterozygous mutation does not result in tumor

acquired mutation of the normal paired gene (loss of heterozygosity/LOH)  
results in tumor

## 2. DNA/mismatch repair genes

make proteins that proofread DNA

defective/mutated gene allows oncogenes and defective (other) tumor repair genes to be produced

HNPCC DNA repair gene defects in Lynch syndrome colon cancer

5% of colon cancers, some endometrial

## 3. suicide/programmed cell death/apoptosis gene

apoptosis: regulated/programmed cell death

main mechanism by which abnormal cells (damaged DNA) are eliminated

avoids overpopulation by contact inhibition of replication

p53 is the main gene responsible for this function in most cells

occasionally mutation is inherited

eg: Li Fraumeni syndrome (LFS): soft tissue and bone sarcomas, brain, breast, adrenal, leukemia

many (50% of human cancers) sporadic cancers with defective p53

chromosome segregator genes

stabilize the cell division mechanism

eg BUB1

examples

RB1: retinoblastoma, multiple others

p53: LiFraumeni syndrome, multiple others

APC (adenomatous polyposis coli): familial polyposis (FP)

only one with 100% penetrance

MLH1, 2, MSH2, 6, PMS1, 2: non-polyposis colon cancer, gastric, endometrial

BRCA1, 2: breast, ovarian

WT1: Wilms tumor

NF1, 2: nerve and brain, rare colon, melanoma, neuroblastoma

VHL: kidney

bcr-abl: chronic myelogenous leukemia (CML)

N-myc: neuroblastoma

EWS: Ewing's sarcoma

C-myc: Burkett's lymphoma and others

gene-targeted treatments

Herceptin/Trastuzumab

monoclonal antibody

prevents HER2/neu protein from promoting excess growth of cancer cells with overexpressed growth factor receptors on cell surface

Gleevac (STI571)

interferes with bcr-abl (oncogene transducer) protein in CML

almost 100% effective for CML

also effective for GIST

gefitinib/Iressa

oral agent blocks EGF receptors

10% benefit non-small cell lung cancer (NSCLC)

cetuximab/Erbix

EGFR blocker  
added to irinotecan for resistant colon cancer  
repair of defective tumor suppressor genes  
need to get new DNA into cancer cells  
problem: most cancer cells have several oncogene and tumor suppressor gene defects  
experimental viral-delivered normal p53 into tumor cells to slow growth  
modified adenovirus ONYX-015 kills cells with the p53 mutation  
possible use against squamous and others

### **Viral-related cancers**

10-15% of malignancies viral related (80% of liver and cervix)  
hepatitis B and C: hepatoma  
HPV: cervical, perineal (and elsewhere) squamous  
EBV (DNA virus), HTLV (RNA virus): lymphomas & leukemias

### **Physical carcinogens**

ionizing radiation, UV radiation: skin, thyroid, bone blood

### **Chemical carcinogens**

multi-step process with latency period  
initiation: carcinogen reacts irreversibly with DNA  
promotion: slow, reversible action by promoting agent  
progression: maturation of cancer cells to tumor

### **Cancer growth**

usually single cell of origin (exception neurofibrosarcoma in VonRecklinghausen)  
proliferate faster than most normal cells (GI mucosa, WBC faster)  
20-100 day doubling time  
30 divisions, 1 billion cells, 1 year to 1cm size  
growth rate decreases as tumor enlarges (Gompertzian growth)  
reversion to more primitive cell form: pleomorphic, increased mitosis, hyperchromatin, loss  
of contact inhibition  
angiogenesis critical factor in ability to metastasize

### **Metastasis**

highly inefficient, tumor may shed 100 million cells into bloodstream before metastasis  
the shorter the interval to metastasis, the more aggressive the tumor  
metastatic cascade, same steps for lymphatics and capillaries  
motility and invasion: angiogenesis allows cells to enter lymphatics or veinules  
transport: cells must get past defenses  
antibodies, complement, natural killer cells, macrophages

- mechanical stresses: turbulence, poor nutrition, low oxygen
- arrest and extravasation at target lymph node or organ
- LN cell enters subcapsular space, then sinusoids
- cellular adhesion molecules (CAM): I-CAM, M-CAM (cadherins), integrins, cell surface lectins, lectin binding glycoproteins (cathepsin D prognostic indicator in breast)
- different levels of adhesion molecules in different tissues may explain metastatic patterns
- passage through subendothelial basement membrane
- tumor cell produces proteolytic enzymes, plasminogen activator, metalloproteins, cathepsins
- establishment of new growth
- primitive autonomous growth factors
- new angiogenesis

### **Biological response modifiers**

- augment host natural defenses
- cytokines produced & secreted by cells
  - interleukins and interferon alpha key regulatory cytokines
  - IL-2: lymphokine from activated T-cells
    - binds to cell surface receptors on activated T-cells -> proliferation
    - activates natural killer cells
    - single agent use against melanoma, renal cell carcinoma
    - combination with chemo agents
  - interferon alpha: activates natural killer cells
  - modulates antibody production by B-cells
  - induces major histocompatibility antigens on tumor cell surface
  - adjuvant therapy for node positive melanoma
- tumor necrosis factors alpha and beta
  - from activated macrophages
  - activate osteoclasts
  - fibroblast growth factor
  - anti-viral
  - cancer cachexia
- hematopoietic growth factors:
  - G-CSF, GM-CSF
  - stimulate bone marrow progenitor cells to become WBCs
  - erythropoietin: proliferation of RBC precursors

### **Chemotherapy**

more rapidly dividing cells more susceptible to cytotoxic agents effect at vulnerable stage of cell cycle

- normal tissue (gut mucosa, bone marrow) with rapid turnover susceptible to injury
- different drugs act at different phases of cell cycle

rationale for combination drug therapy

large tumors are relatively resistant to chemotherapy

more cells in resting phase (G<sub>0</sub>), less sensitive to toxicity

less reliable penetrance of drug

most drugs kill a fixed proportion of cells, not a fixed number

all chemotherapy drugs except alkylators classified by timing in cell cycle

phase-dependent drugs

most antimetabolic agents act in the DNA synthetic (S) phase

interfere with enzymes necessary for DNA/RNA replication

or act as false substrates during replication

eg: adriamycin, 5FU, gemcitabine

methotrexate: inhibits dihydrofolate reductase

taxanes & vinca alkaloids act in the mitotic (M) phase

interfere with the spindle that separates the chromatids

taxane eg: taxol, taxotere

vinca alkaloids (vincristine, vinblastine):

bind to tubulin and inhibits the metaphase of mitosis

non-phase dependent drugs

alkylating agents

act at any phase of the cell cycle

linear dose response curve

eg: cytoxan, platins, nitrosoureas, nitrogen mustard

equally toxic any cell cycle phase including resting

eg: cyclophosphamide, cisplatin, 5FU

cisplatin: inhibits DNA synthesis by cross linking DNA strands

anthracyclines: doxorubicin inhibits RNA synthesis by intercalating  
between DNA base pairs

general side effects

GI toxicity, nausea and vomiting

bone marrow toxicity

alopecia

gonadal effects (hypogonadism, sterility)

hyperuricemia

specific side effects

adriamycin: cardiotoxicity

bleomycin: pulmonary fibrosis

inhibits DNA polymerase, causing breakage of single stranded DNA

doxorubicin: cardiomyopathy  
methotrexate: liver damage, kidney damage  
cyclophosphamide: hemorrhagic cystitis  
5FU: skin pigmentation  
cisplatin: nephrotoxic

tumors potentially curable by chemotherapy

germ cell tumors  
choriocarcinoma  
Hodgkin's lymphoma  
Wilms tumor

tumors with significant response to chemo

breast  
ovarian  
lymphoma  
osteosarcoma

poorly responsive tumors

pancreatic  
melanoma  
soft tissue sarcomas  
colorectal  
gastric

## **Radiotherapy**

most RT done with high-energy photons (gamma or X-rays), deeper penetration  
neutrons higher relative biological effectiveness (RBE), 3X photons  
hyperfractionation allows 10-15% higher dose  
Gray: energy (joules) absorbed/unit mass (1j/kg)  
1Gy = 100 rads, 1 rad = 1 cGy  
radiation affects the nucleus, most cells don't die until they divide  
kidney, liver, lung, lymphocytes sensitive; muscle, bone, nerve radioresistant  
treatment more effective through air spaces, compromised by bone  
electron beams from linear accelerator useful for superficial cancers  
skin, head and neck, previously photon irradiated sites  
intensity modulated radiotherapy (IMRT): computer based planning for tight dose  
conformity around target, allows higher dose, spares surrounding  
brachytherapy  
seed implants or afterloading catheters  
effective for GU

## Hormonal therapy

breast cancer

50-60% of breast cancers are ER/PR positive

70% of receptor-positive tumors respond to hormonal manipulation

only 5% of ER- tumors respond

selective estrogen receptor modulators (SERMs)

weak estrogen analog competitively binds ERs, blocks estrogen binding

tamoxifen, raloxifene, fulvestrant

can be used in pre and postmenopausal

aromatase inhibitors: block conversion androgen to estrogen

postmenopausal only (ovary compensates in premenopausal)

non-steroidal: anastrozole, letrozole

steroidal: exemestane

premenopausal: ovarian ablation option

## Cancer syndromes

Klinefelters: XXY 47, 20X incidence male breast cancer

(no breast cancer Turner's or Downs)

Cowden's: PTEN, hamartomatous colon polyps, 50% breast cancer

LiFraumeni: 70% have defective p53 tumor suppressor, autosomal dominant; bone and soft tissue sarcoma, breast, brain cancer, gastric cancer

Lynch (HNPCC): multiple mismatch repair genes (MSH, MLH, PMS), 3% of all colorectal cancers (15% with a family history), early colon cancer (most right), endometrial, upper GU (renal cell) cancer follow with colonoscopy, urinalysis, vaginal ultrasound

FAP (APC mutation)/Gardner's: polyposis colon cancer, gastric cancer (diffuse form), 2% lifetime risk thyroid cancer

Gardner's: osteomas, exostoses, desmoid, 33% duodenal polyps, 25% gastric

periampullary carcinoma second most common cause of death after colon Ca

Turcot's (variant of FAP?): medulloblastoma

Peutz-Jegher: serine/threonine kinase 11 (STK11), autosomal dominant, hamartomatous GI polyps, pigmented lesions buccal mucosa, lips, digits

intestinal obstruction, intussusception, bleeding, malignant potential

stomach lesions in 1/4, colorectal 1/3

Juvenile polyposis: pancreatic cancer

Marfan's: elastin defect, aneurysms, hyperflexibility

(no skin healing problem v Ehler's Danlos)

WT: Wilms tumor, embryonal renal tumor, aniridia, GU abnormalities

Rb1: retinoblastoma, sarcoma, brain tumor, malignant melanoma

TSC: tuberous sclerosis, multiple hamartomas, renal cell carcinoma, astrocytoma

Gastric cancers: LiF, FAP, HNPCC

familial melanoma: CDKN2A

neurofibromatosis type 2: neural tumors, acoustic neuroma, meningioma, glioma, ependymoma

Werner's: adult progeria, autosomal recessive, atherosclerosis, cancers, sarcomas

PTH: nevoid basal cell carcinoma

SDHD: paragangliomas

PRSS1: hereditary pancreatitis and pancreatic cancer

NOD2, IBD2: associated with Crohn's

Pheochromocytoma

30% of pheos hereditary association

RET protooncogene: adrenal medullary cell proliferation

RET: MEN 2A: MTC, pheo, parathyroid hyperplasia

B: " " (no para)

30% of pts with MEN2 develop pheo

100% with RET develop MTC, prophylactic thyroidectomy as early as 6y

VH-L: tumor suppressor gene, 15-20% incidence pheo

neurofibromatosis: 5% incidence

## Summary/groups

thyroid

FAP, Gardner's

Crohn's

breast

Klinefelter's

Cowden's

LiFraumeni

gastric

LiFraumeni

FAP, Gardners

Peutz-Jegher's

renal

Lynch

Tuberous sclerosis

Wilms

melanoma

Rb1

CDKNZA

pheo

RET

VH-L

neurofibromatosis

## References:

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