

Biomarkers of cancer

By
Dr. Gouse Mohiddin Shaik

Biomarkers of cancer

- In this section we will discuss...
- Introduction
- Types of cancer biomarkers
- Application of cancer biomarkers
 - PSA
 - AFP

Biomarkers of cancer

- Any measurable alterations specific to cancer cell either at DNA, RNA, protein or any metabolite level can be referred as cancer biomarker
- An ideal biomarker for cancer is expected to have applications in
 - Determining predisposition
 - Early detection
 - Assessment of prognosis
 - Assessment of therapeutic intervention
 - Drug development

Biomarkers of cancer

- Any measurable alterations specific to cancer cell either at DNA, RNA, protein or any metabolite level can be referred as cancer biomarker
- An ideal biomarker for cancer is expected to have applications in
 - Determining predisposition
 - Early detection
 - Assessment of prognosis
 - Assessment of therapeutic intervention
 - Drug development

Biomarkers of cancer

- Types of cancer biomarkers

Types of cancer biomarkers

Genetic biomarkers – PTEN tumor suppressor gene status, mutations, oncogenes

DNA biomarkers – gene amplifications, microsatellite instability, mt.DNA, viral DNA

RNA biomarkers - microRNAs

Protein biomarkers – B7 coregulatory ligands, increased serum lactate dehydrogenase, high-motility group protein A2, HSP 90

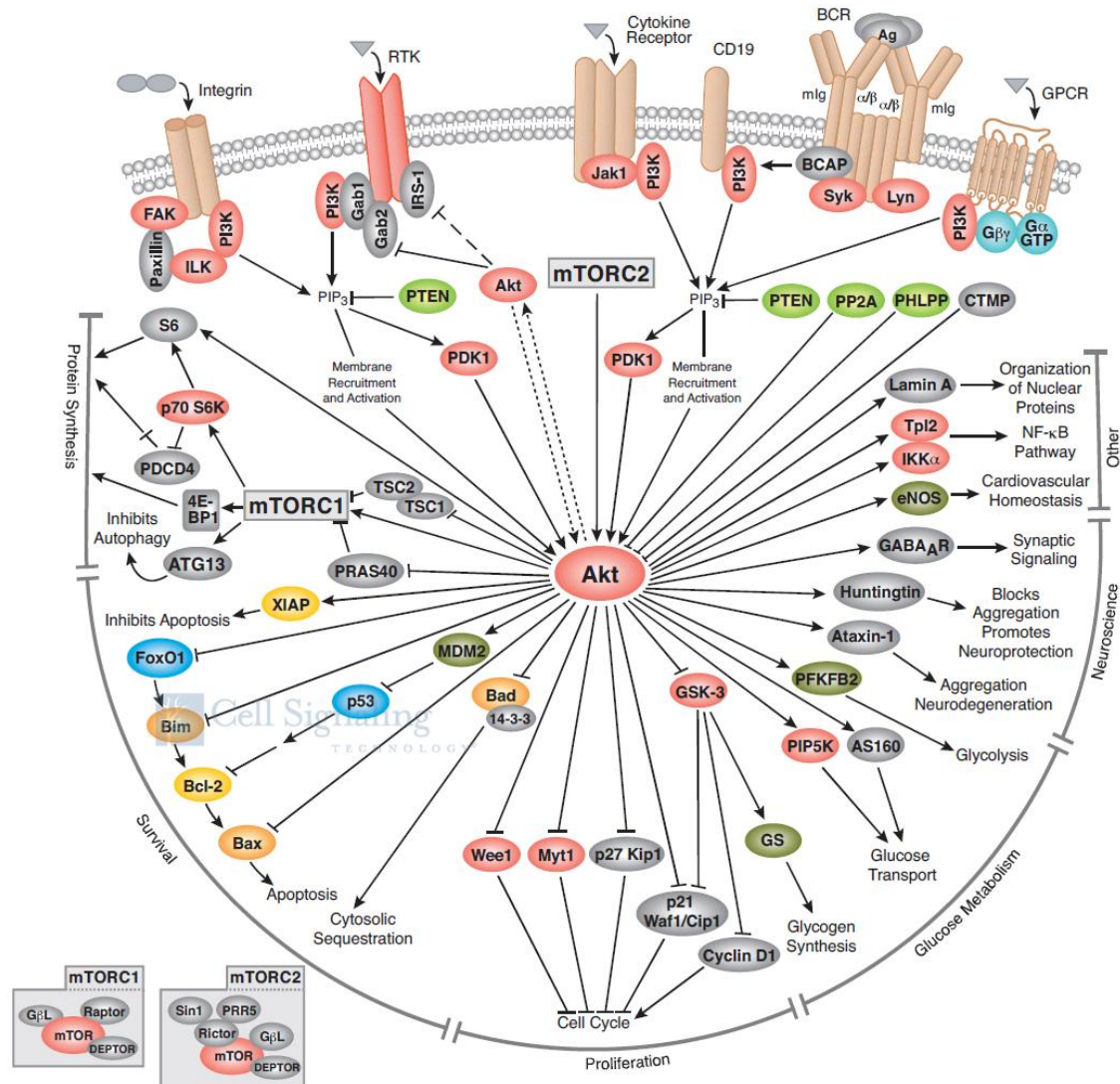
Metabolic biomarkers – hypoxia induced factor -1

Immunological biomarkers – T-cells and cytokine profile

Biomarkers of cancer

- **Genetic biomarkers**
 - PTEN gene (phosphatase and tensin homologue)
 - Most commonly lost tumor suppressor in human cancers
 - Encodes Phosphatidylinositol-3,4,5-triphosphate 3-phosphatase protein
 - Controls cell cycle by inhibiting AKT signaling pathway

Biomarkers of cancer

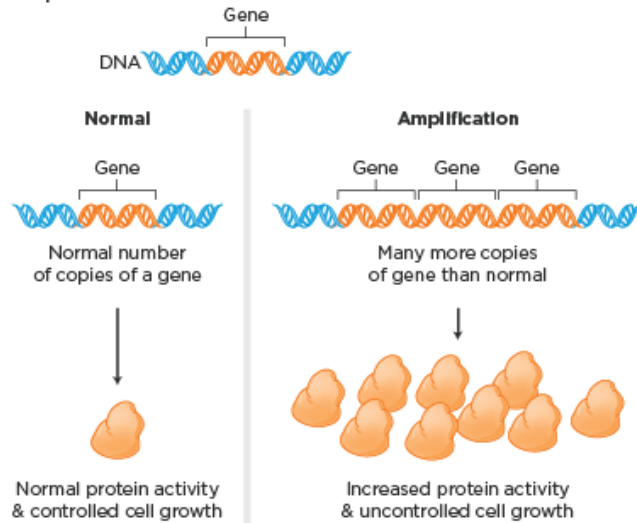


Biomarkers of cancer

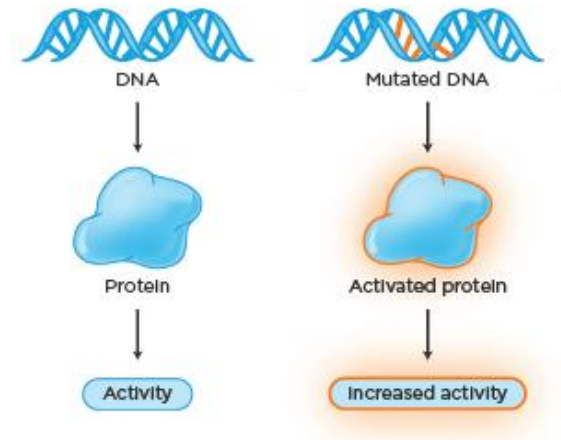
- DNA biomarkers
 - Gene amplification
 - Duplication of genes to over-express some genes
 - Microsatellite instability
 - Defect leading to altered number of tandem repeats in genome
 - Mutations
 - Any change of DNA that can be inherited

Biomarkers of cancer

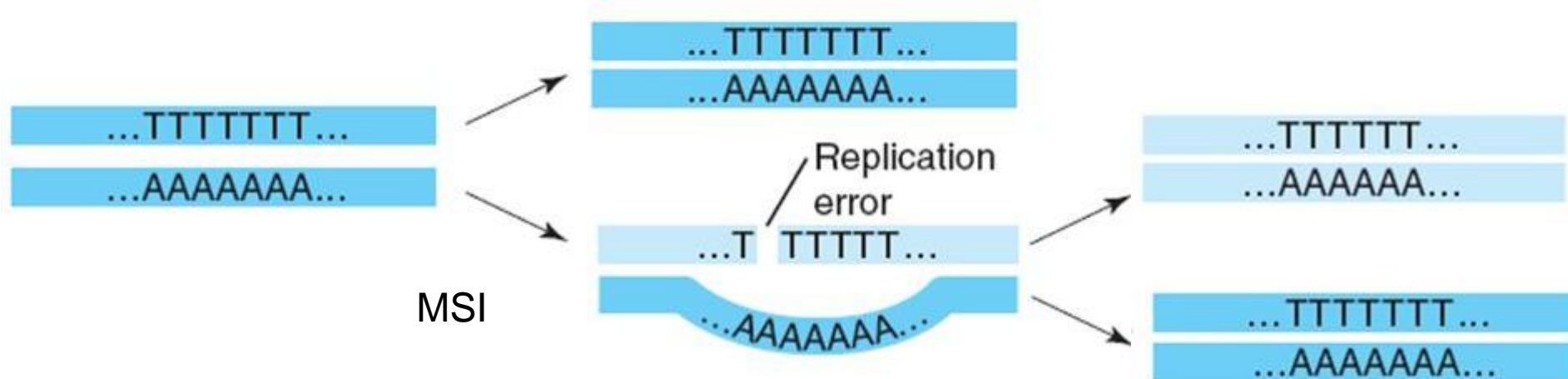
Amplification



Activating Mutation

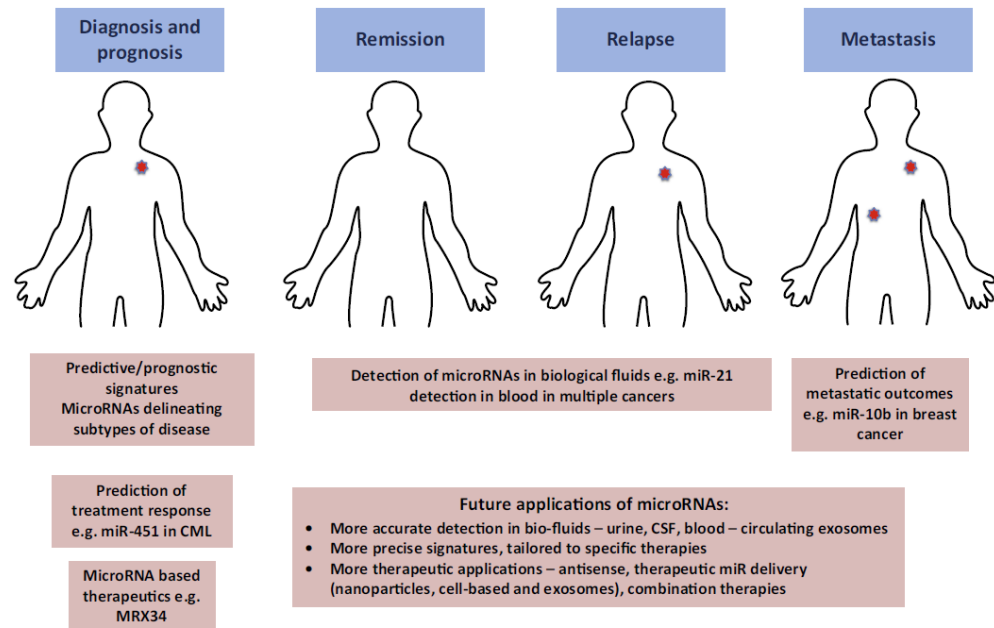


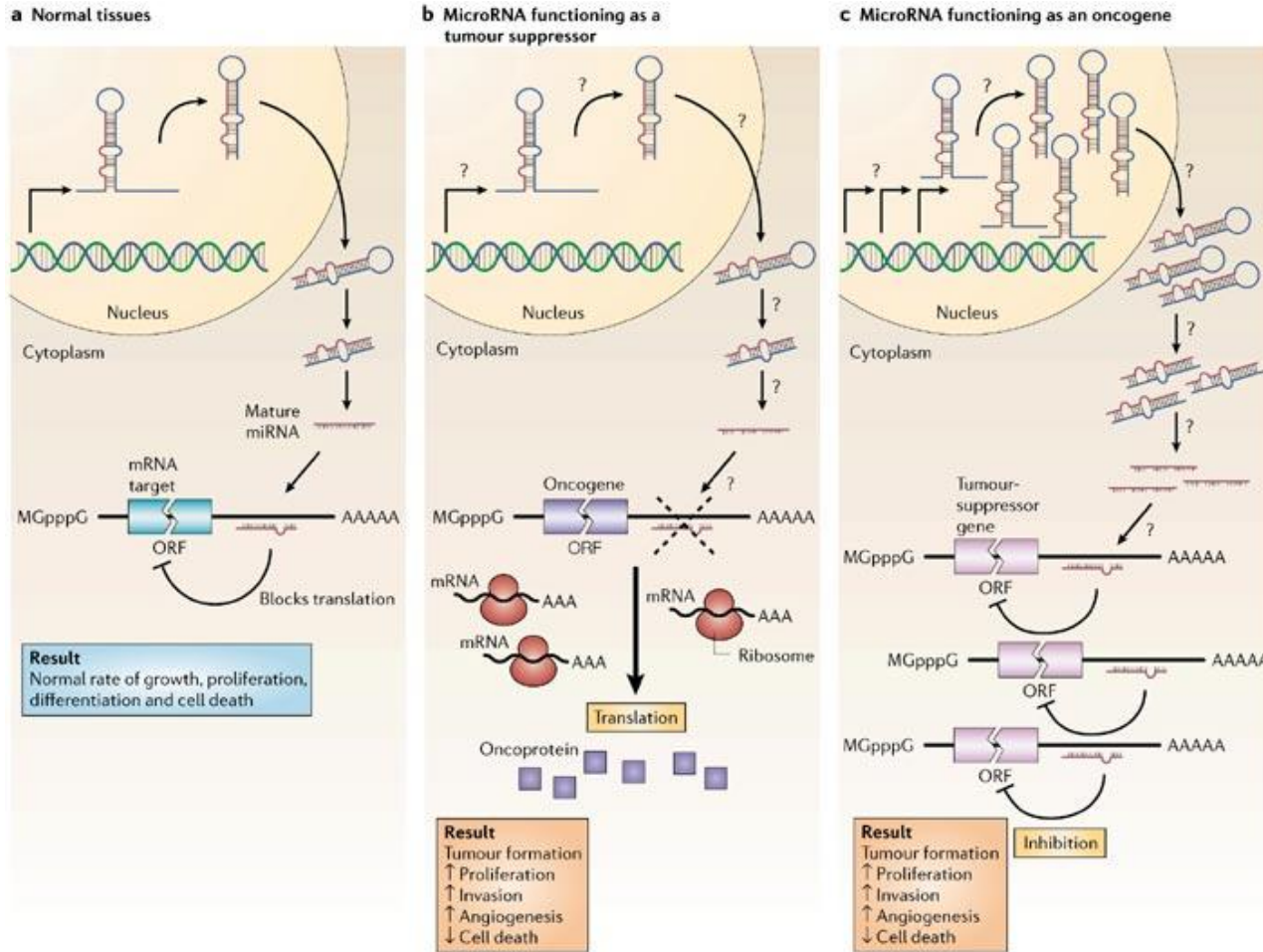
MSI



Biomarkers of cancer

- RNA biomarkers
 - Micro RNAs
 - Small family of non-coding RNAs that function in regulation of gene expression
 - Needed for normal functioning of genes
 - Can act a tumor suppressors / oncogene

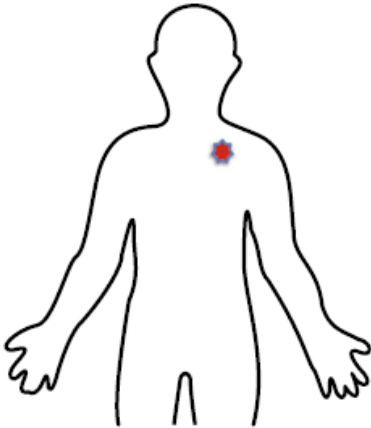




Copyright © 2005 Nature Publishing Group
 Nature Reviews | Cancer

Esquela-Kerscher *et al. Nature Reviews Cancer* 6, 259–269 (April 2006) | doi:10.1038/nrc1840

Diagnosis and prognosis

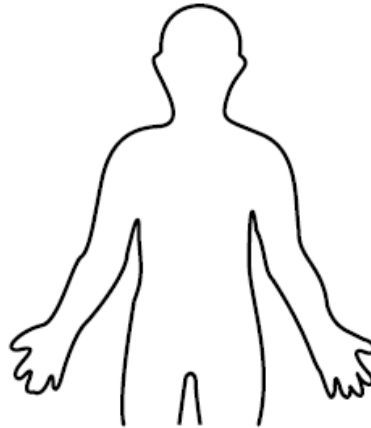


Predictive/prognostic signatures
MicroRNAs delineating subtypes of disease

Prediction of treatment response
e.g. miR-451 in CML

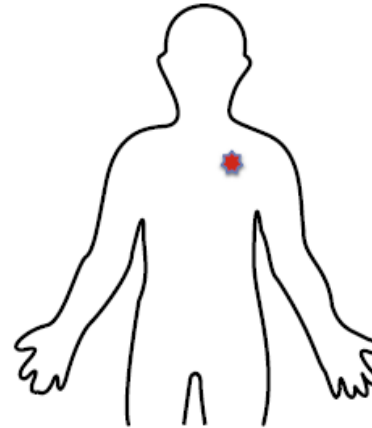
MicroRNA based therapeutics e.g. MRX34

Remission

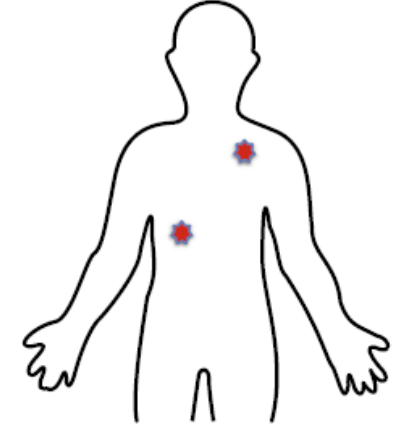


Detection of microRNAs in biological fluids e.g. miR-21
detection in blood in multiple cancers

Relapse



Metastasis



Prediction of metastatic outcomes
e.g. miR-10b in breast cancer

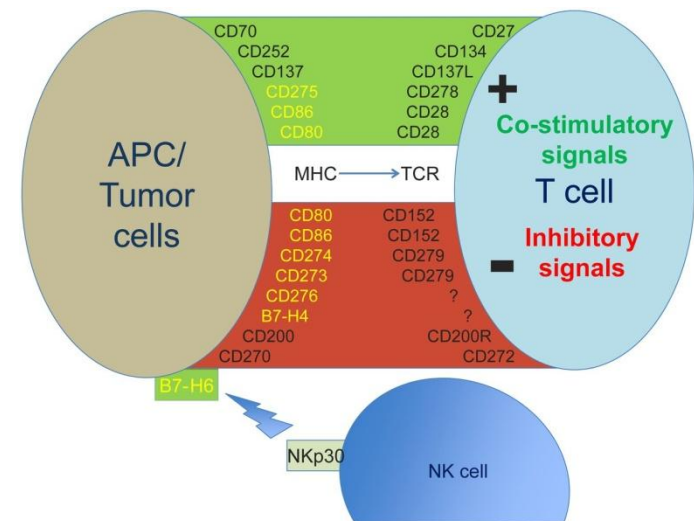
Future applications of microRNAs:

- More accurate detection in bio-fluids – urine, CSF, blood – circulating exosomes
- More precise signatures, tailored to specific therapies
- More therapeutic applications – antisense, therapeutic miR delivery (nanoparticles, cell-based and exosomes), combination therapies

Biomarkers of cancer

- Protein biomarkers
 - B7 co regulatory ligands
 - Generally found on activated antigen presenting cells
 - By binding to different surface proteins on T cell can initiate +ve or -ve signals

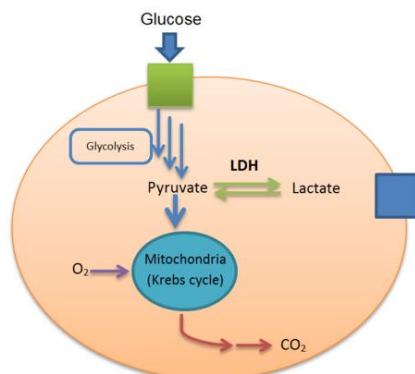
B7 family	Extracellular domain	Co-signaling nature	Receptor
B7.1 (CD80)	IgV+IgC	Co-stimulation	CD28
		Co-inhibition	CTLA-4 (CD152)
		Co-inhibition	B7-H1 (CD274)
B7.2 (CD86)	IgV+IgC	Co-stimulation	CD28
		Co-inhibition	CTLA-4
B7-H1 (PD-L1, CD274)	IgV+IgC	Co-inhibition	PD-1 (CD279)
		Co-inhibition	B7.1
		Co-stimulation	Unknown
B7-DC (PD-L2, CD273)	IgV+IgC	Co-inhibition	PD-1
B7-H2 (ICOSL, CD275)	IgV+IgC	Co-stimulation	ICOS (CD278)
		Co-stimulation	CD28
B7-H3 (CD276)	IgV+IgC+IgV+IgC (Hu)	Co-stimulation	Unknown
		Co-inhibition	Unknown
B7-H4 (VTCN1)	IgV+IgC	Co-inhibition	Unknown
B7-H5 (VISTA)	IgV	Co-inhibition	Unknown
B7-H6 (NCR3LG1)	IgV+IgC	Co-stimulation	NKp30
B7-H7 (HHLA2)	IgV+IgC+IgV	Co-stimulation	CD28H



Biomarkers of cancer

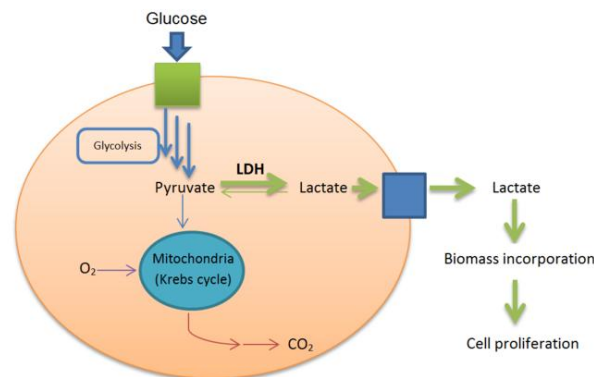
- Protein biomarkers
 - LDH – lactate dehydrogenase
 - LDH involved in tumor initiation
 - In cancer cells glycolysis 200x more. Energy production
 - Warburg effect – leading to lactate fermentation

Normal Cell



Oxidative phosphorylation- high ATP: glucose ratio, low LDH activity in both directions results in high energy production.

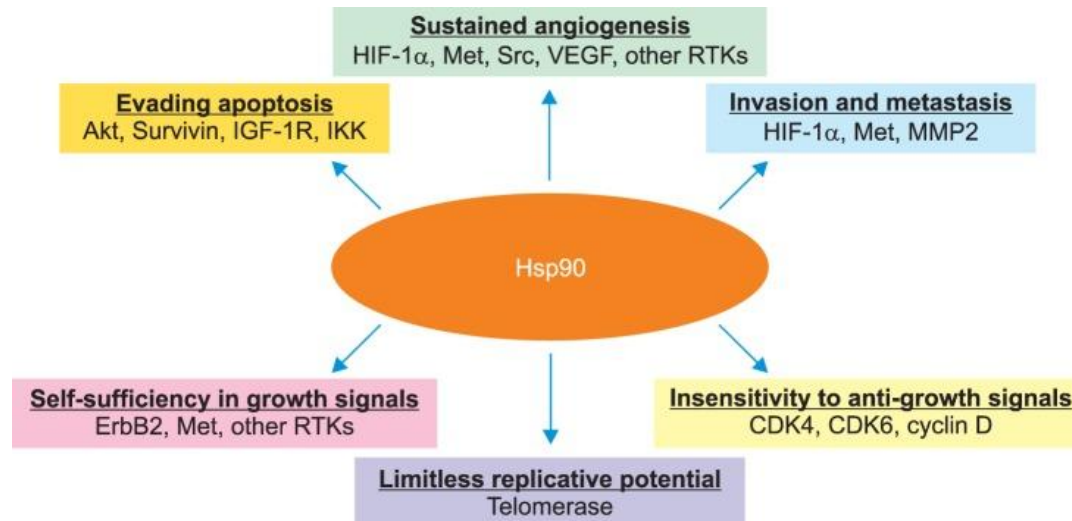
Cancer Cell

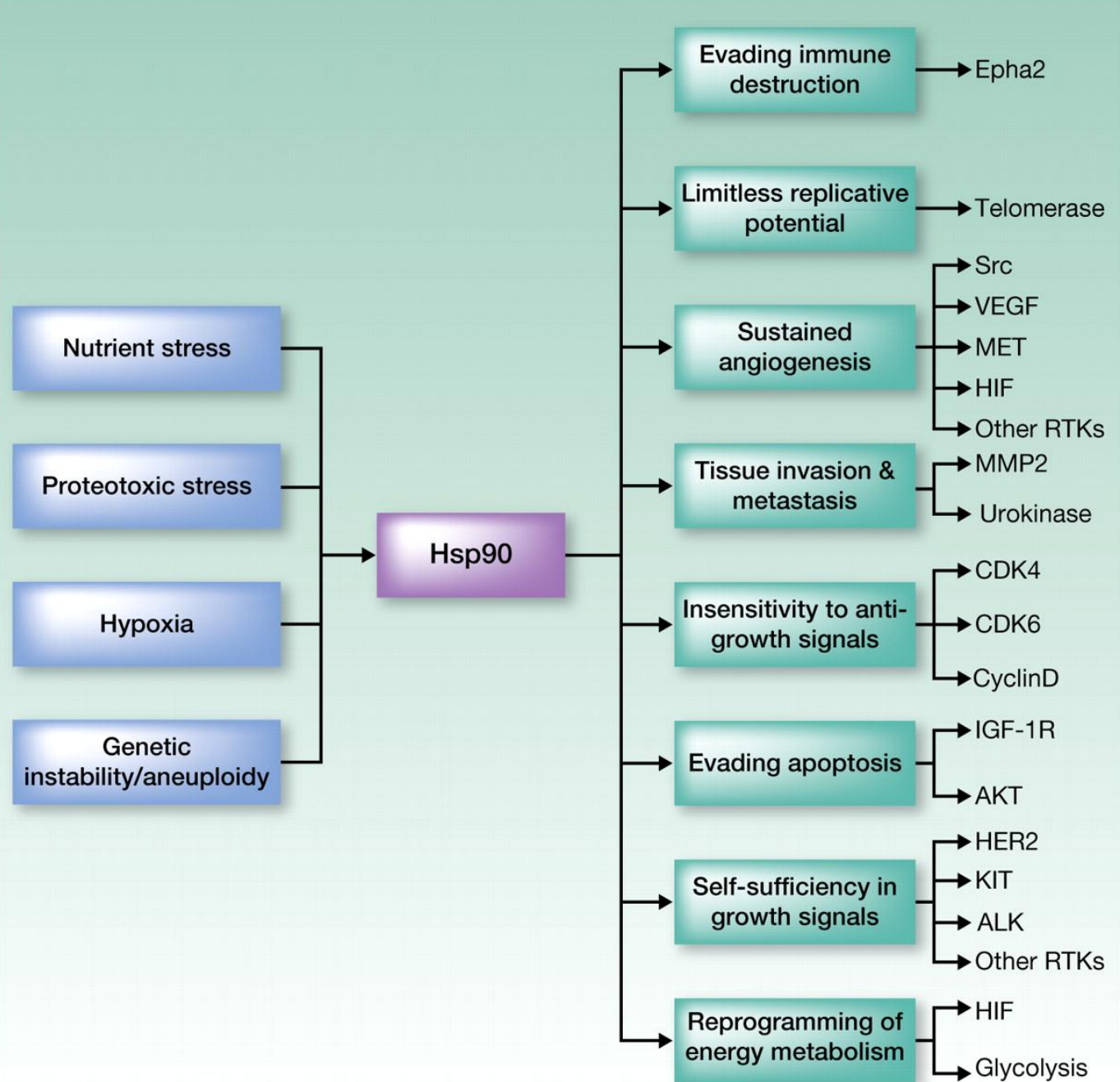


Aerobic glycolysis (Warburg effect) - low ATP: glucose ratio, high LDH activity in one direction. Results in biomass incorporation and cell proliferation.

Biomarkers of cancer

- Protein biomarkers
 - HSP-90
 - Stress activated / regulated protein
 - Functions as chaperon protein, helps other proteins to fold and function properly
 - Many cancer types show high hsp-90

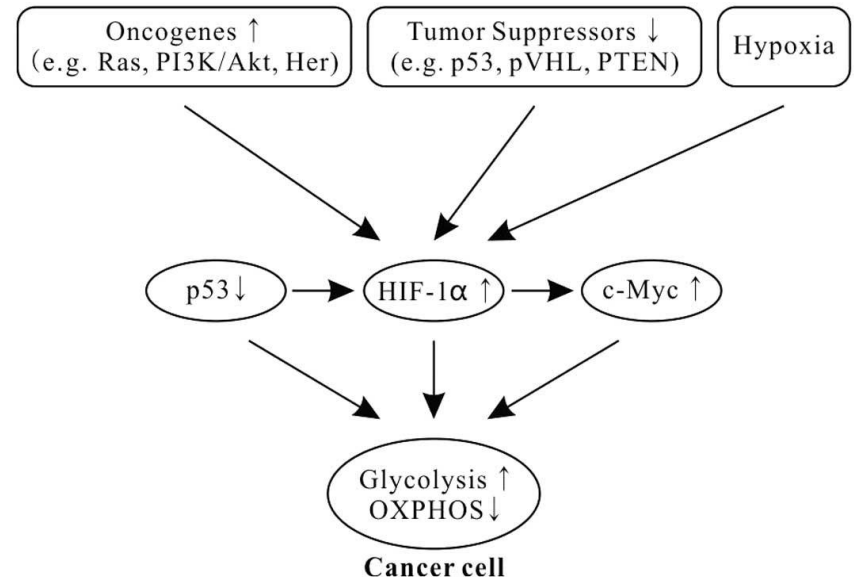
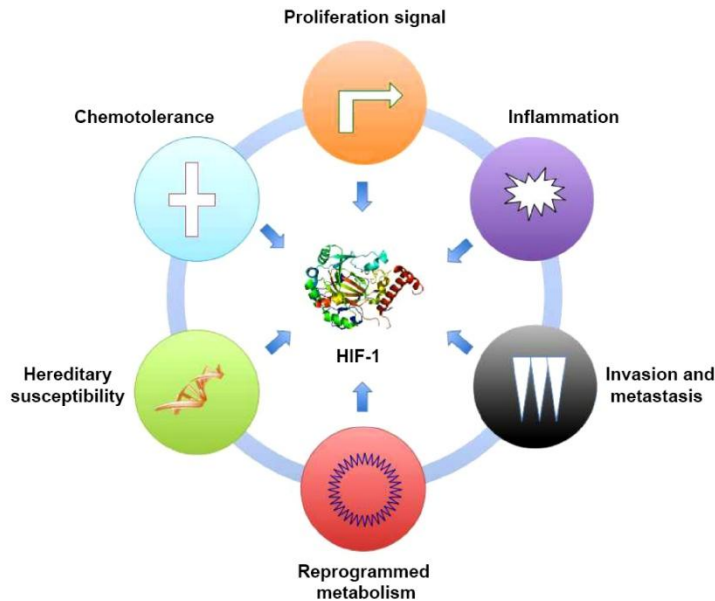




© 2012 American Association for Cancer Research

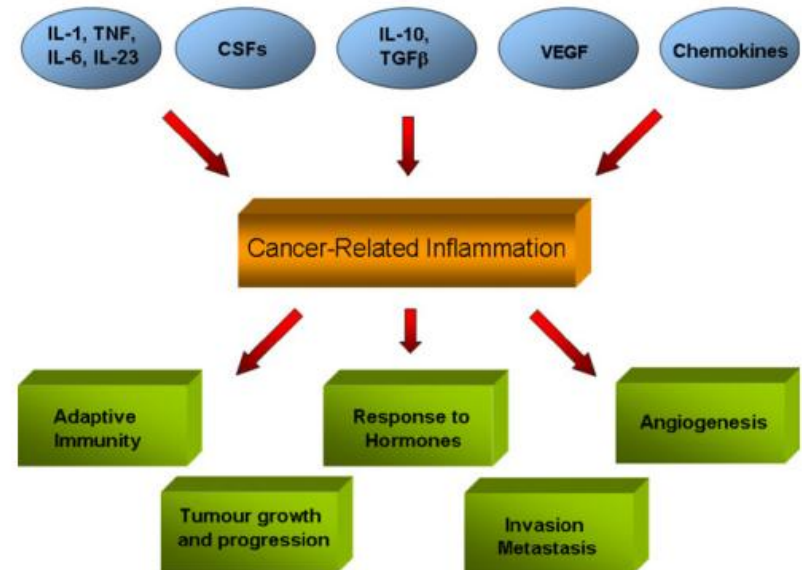
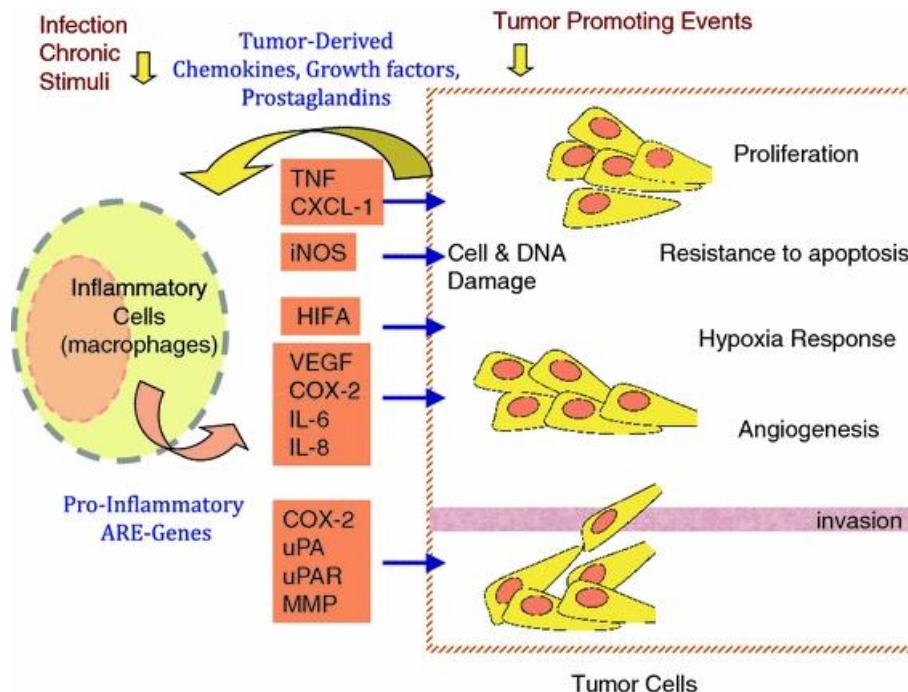
Biomarkers of cancer

- **Metabolic markers**
 - **Hypoxia induced factor 1 (HIF)**
 - HIFs are transcriptional factors that respond to O_2 concentration in cells
 - In cancers decreased O_2 in cells due to high cell division. Activating HIFs



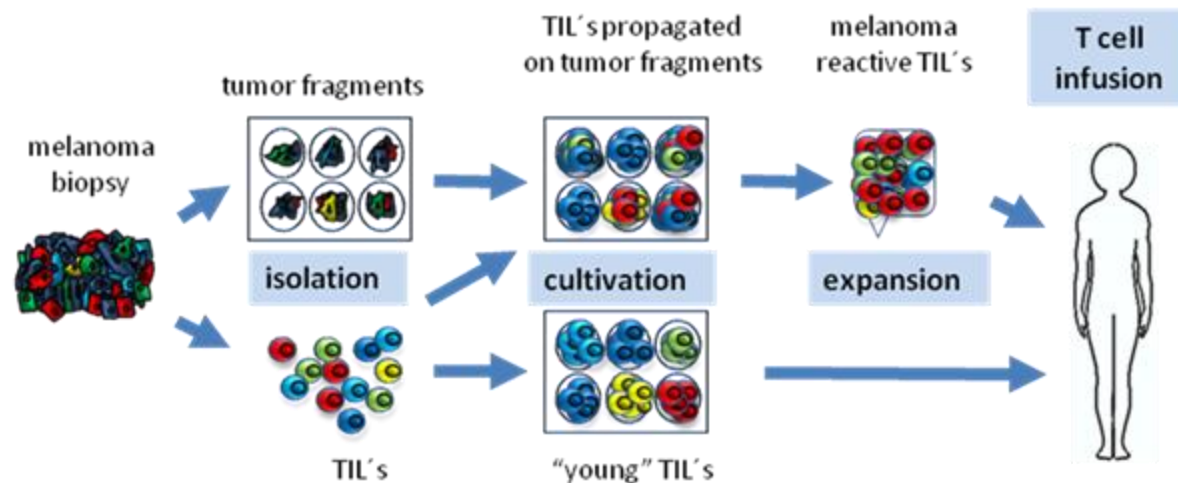
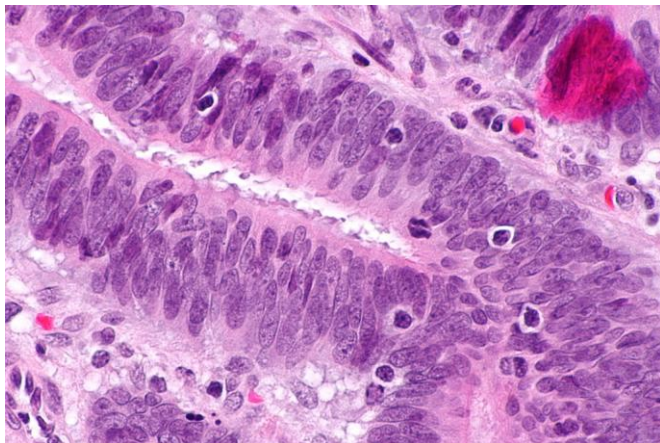
Biomarkers of cancer

- Immunological markers
 - Cytokine profile in cancer
 - Specific profile of cytokines can be a marker of a cancer
 - Pro-inflammatory cytokines promote cancer



Biomarkers of cancer

- Immunological markers
 - Tumor infiltrating lymphocytes (TILs)
 - Can be seen in different parts of tumors
 - Play important role as biomarkers in development of cancer immunotherapies
 - Next generation TILs – genetically engineered

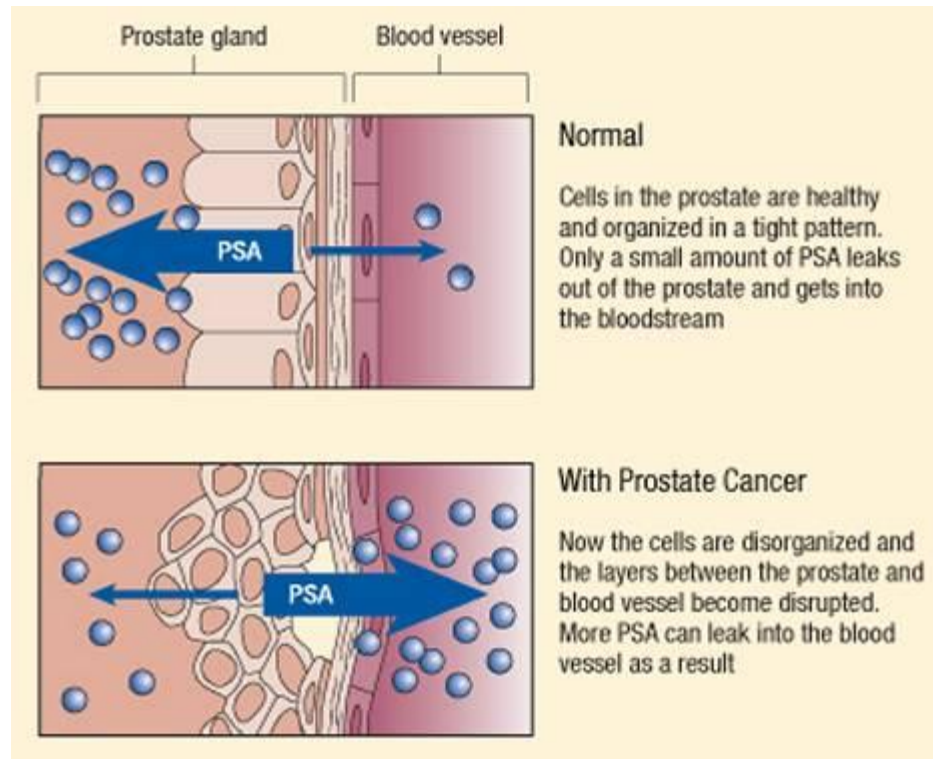


Biomarkers of cancer

- PSA
 - Prostate specific antigen
 - PSA is a protein produced by prostate
 - Belongs to family kallikrein
 - Most of the PSA secreted by prostate is carried out of the body by semen
 - Very minute amount escapes in to blood stream
 - To detect such small amount (ng - pg) high sensitivity assay is needed
 - Monoclonal antibody applied ELISA kits are specific and sensitive

Biomarkers of cancer

- PSA
 - Prostate specific antigen



Biomarkers of cancer

- AFP

- Alpha fetoprotein

- AFP mainly expressed during fetal development
- After birth expression level decreases
- During malignancies expression level increases
- Especially in malignancies associated with liver, ovaries and testicles

Fetus



Testes



Ovaries



Liver



Biomarkers of cancer

- Techniques of detection
 - Will be dealt in separate section

Next class

- Next class.....
 - Biomarkers of cardiovascular diseases