Cancer

- Molecular progression
- Hallmarks
- Metabolism

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Abstract

Cancer is a class of disorders characterized by uncontrolled cell division, deregulated social behavior ensuing invasion of neighboring tissue cells, & finally metastasis. The process of carcinogenesis is multi-step – a series of genetic, epigenetic & chromosomal changes that confer adaptive hallmarks to internal & environmental proliferative constraints – a true "systems" disease occurring by somatic evolution.

Definitions

Hippocrates described several kinds of cancers. He called **benign tumors** (enclosed, does not invade surrounding tissue) *oncos*, Greek for swelling, and **malignant tumors** (show aggressive behavior characterised by local invasion or distant **metastasis**) *carcinos*, Greek for crab or crayfish.

Carcinoma (epithelial cells), **Sarcoma** (connective tissue), **Leukemia** (blood & bone marrow cells), **Glioma** (brain cells)…

Molecular Origins…

Cancer is basically a manifestation of

- Stuck Accelerators
- Defective Brakes

causing deregulated inter- and intra-cellular signaling.

Mutations in genes that encode proteins that maintain structural integrity also aid the process.

More Definitions

Proto-oncogene – Gene which when undergoes 'gain of function' mutation (to become an oncogene – the stuck accelerators) confers growth advantage to the cell. cMyc, Ras.

Tumor Suppressor gene – Gene … 'loss of function' (to become defective breaks)… p53, VHL.

These mutations are often caused by chemicals or physical agents called **carcinogens**, while the others occur spontaneously.

Cancer is a consequence of a microevolutionary process that takes place in the somatic microenvironment.

Our cells are cooperative*. Each cell behaves in socially responsible manner, resting, dividing, differentiating, or dying as needed for the good of the organism. Molecular disturbances to this harmony is the trouble!

* A phenomenon called 'cell competition' is coming into surface now which is that cells compete with each other (not by fighting for growth/survival factors, but through a mechanism for comparing fitness), and that fitter/healthier cells 'actively' kill weak/less-healthier cells by inducing apoptosis.

Human body – more than 10^{14} cells;
billions of cells experience mutations every day, potentially disrupting the social controls.

A somatic mutation may give one cell a selective advantage, allowing it to divide more vigorously than its neighbors and to become a founder of a growing mutant clone.

Successive rounds of mutation, competition, and natural selection → Tumorigenic potential!

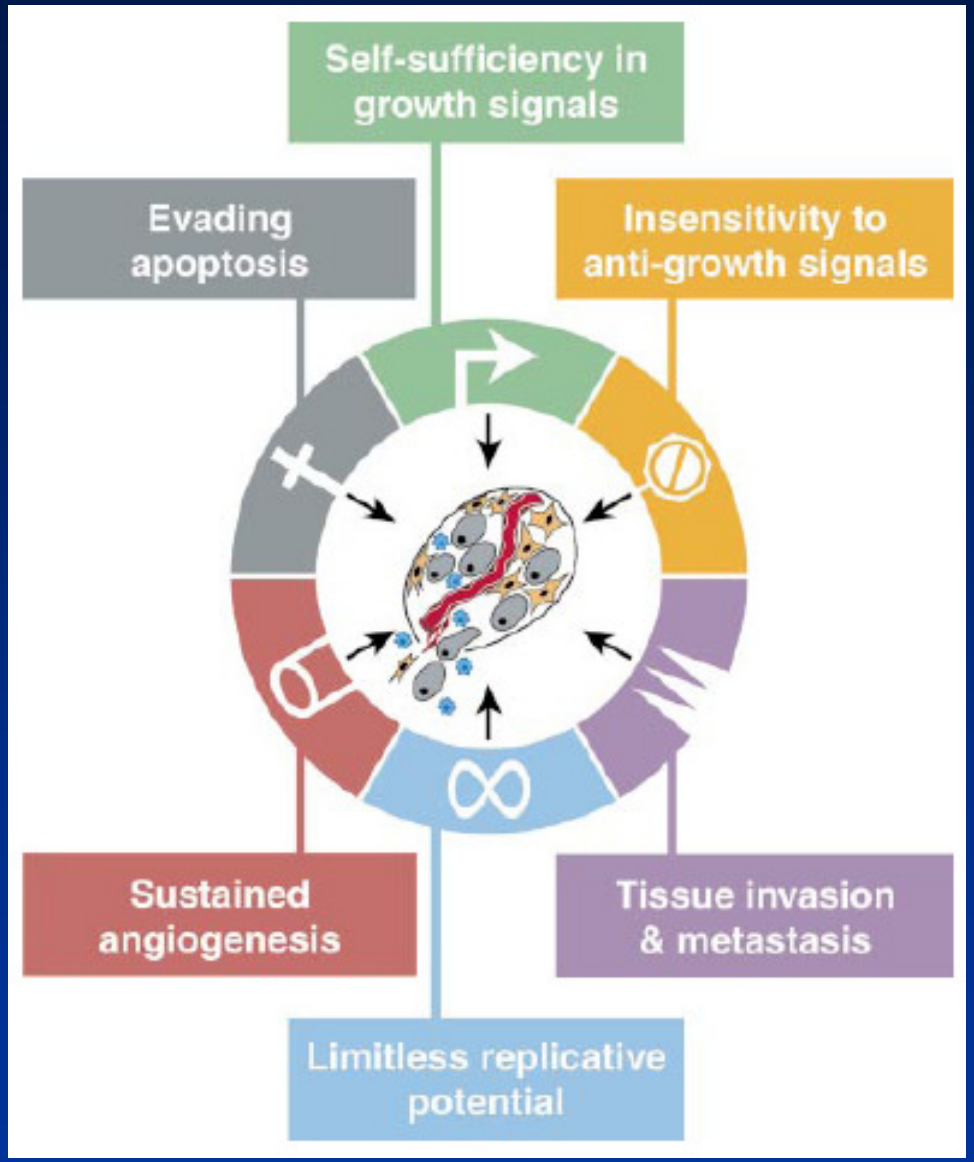
Cancer is also characterized by ‘genetic instability’; an “optimum” level of it exists for the development of cancer, making a cell mutable enough to evolve readily (& dangerously), but not so mutable that it dies#.

Evolvabiltiy* resides in the mutated cells, that confers a tendency to harbor genetic changes, which in turn increases the chance of stumbling upon an improved or novel trait.

A property of the telomerase enzyme (to be discussed later) is responsible for this to a great extent.

* Evolvability is the capacity to evolve, to generate heritable, selectable phenotypic variation

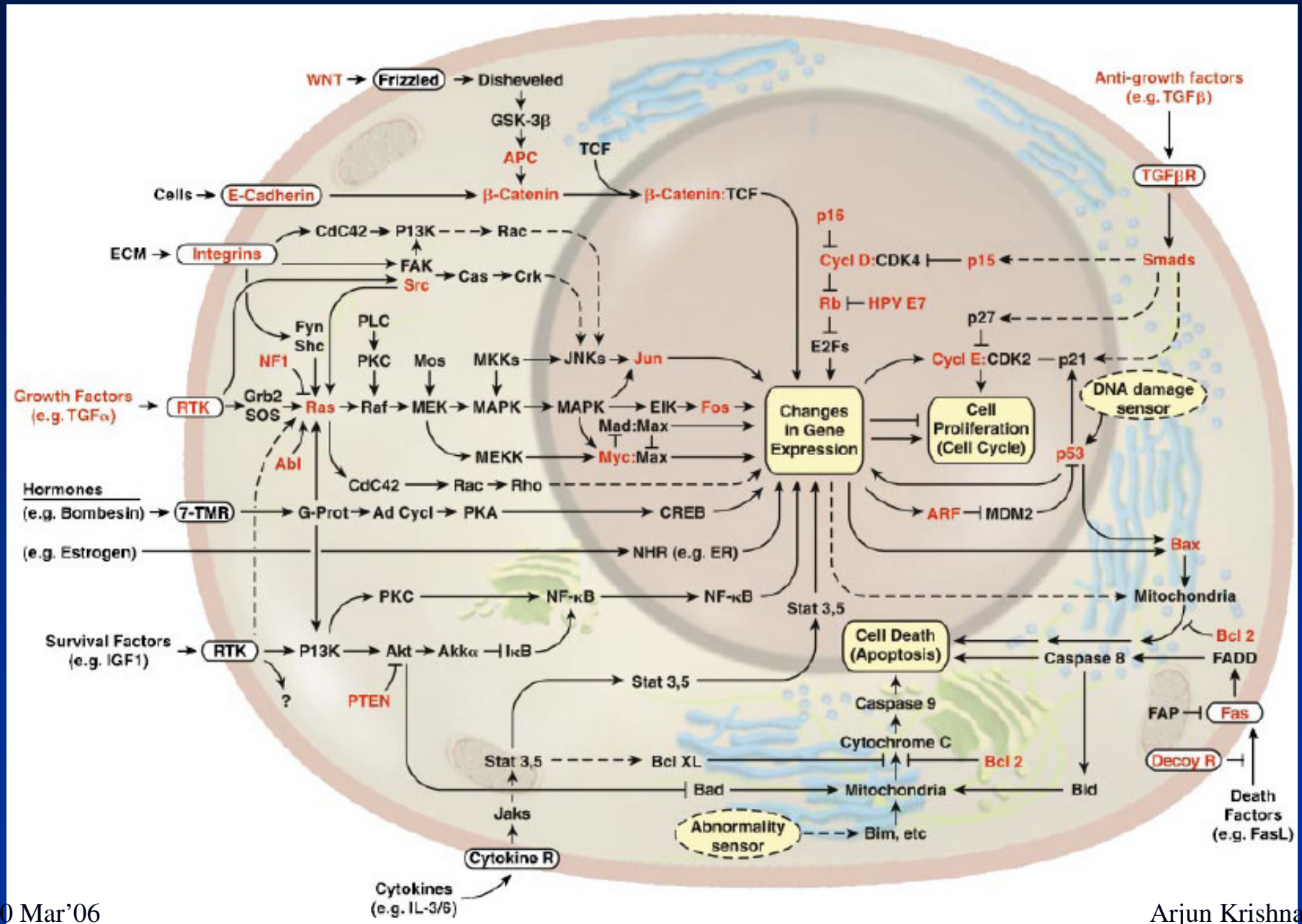
Hallmarks



The six hallmarks of cancer that Hanahan & Weinberg proposed.

Cell (2000) 100:57-70

The Integrated Circuit of the Cell – a sample!



Self-sufficiency in growth/survival signals

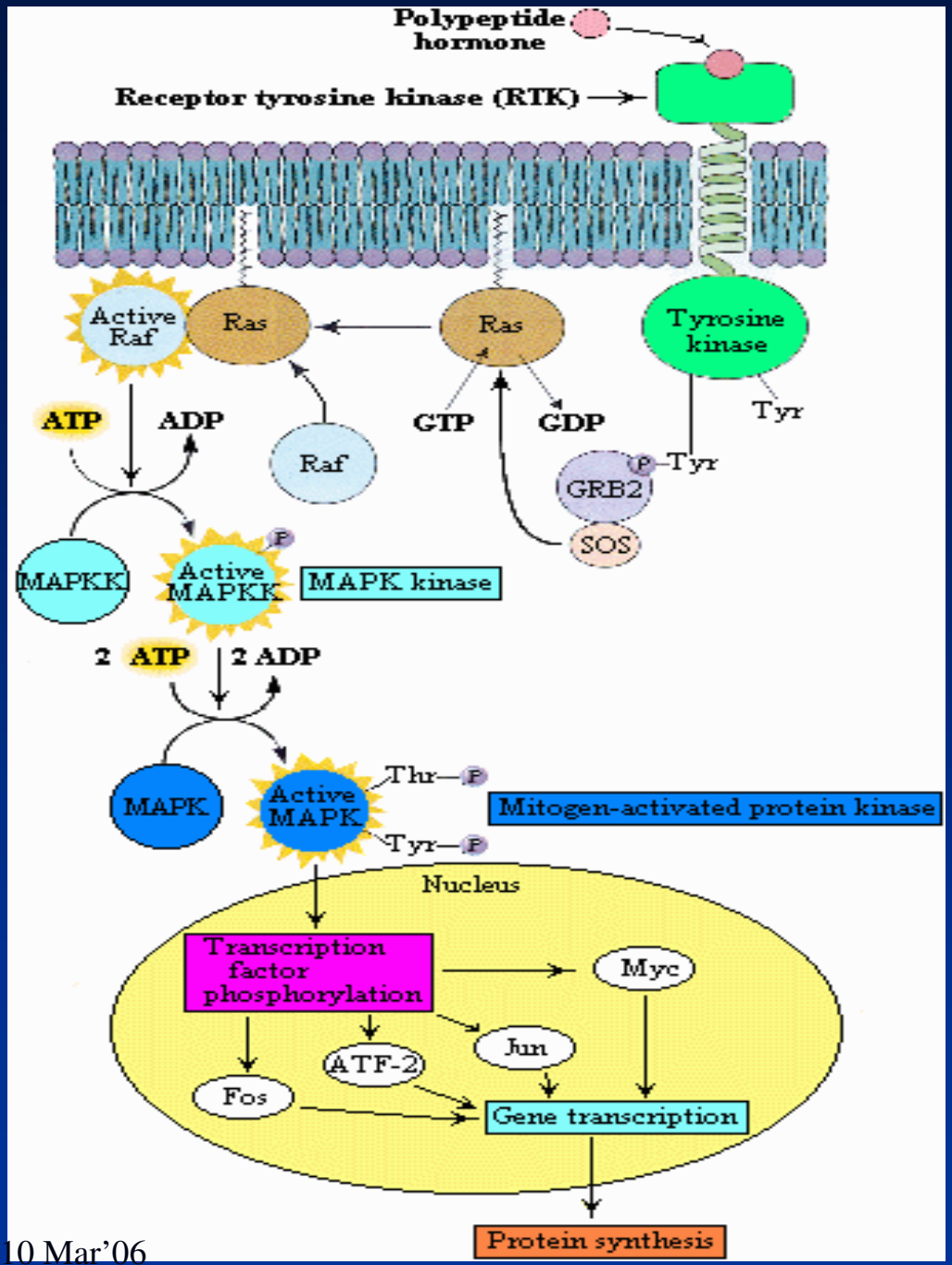
Normal cells

Mitogenic growth signals (Heterotypic signaling) → Quiescent state to active proliferative state.

Tumor cells

Generate many of their own GS, thereby reducing their dependence on stimulation from their normal tissue microenvironment.

Synthesize GS to which they are responsive – a positive feedback loop – autocrine stimulation.



The SOS-Ras-Raf-MAPK pathway

Insensitivity to anti-growth signals

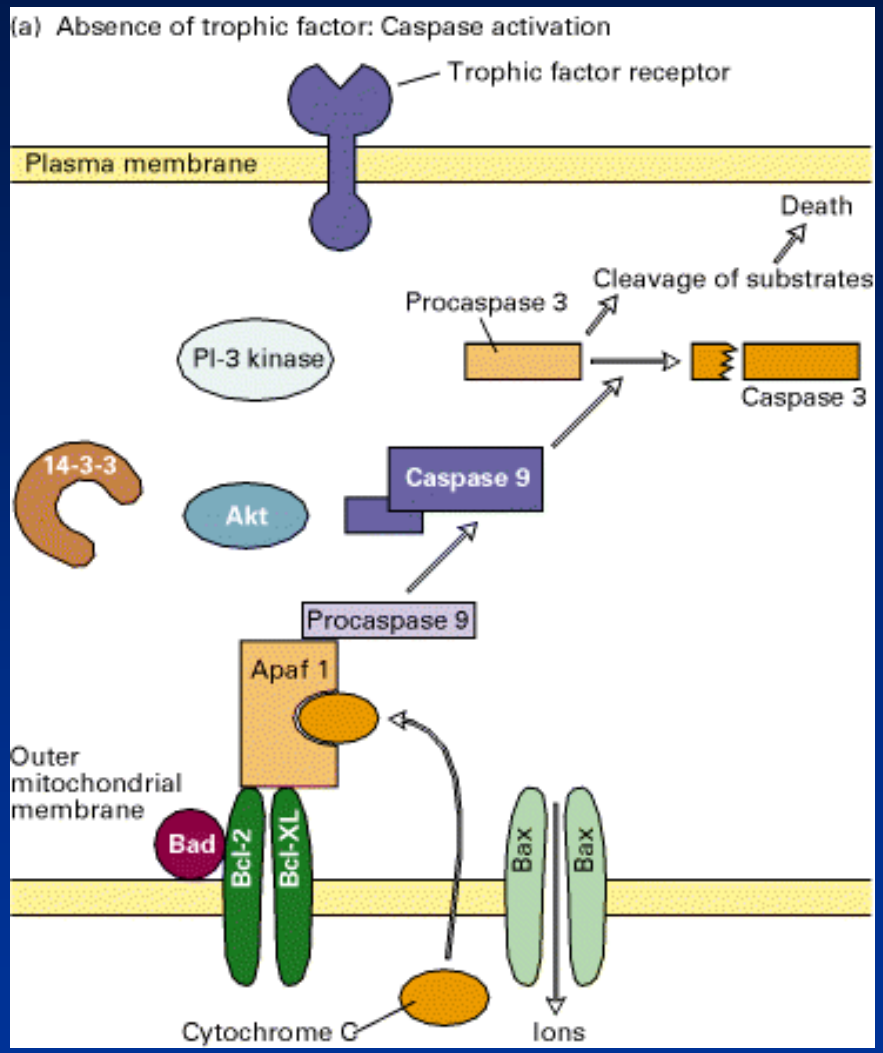
Cell quiescence & tissue homeostasis

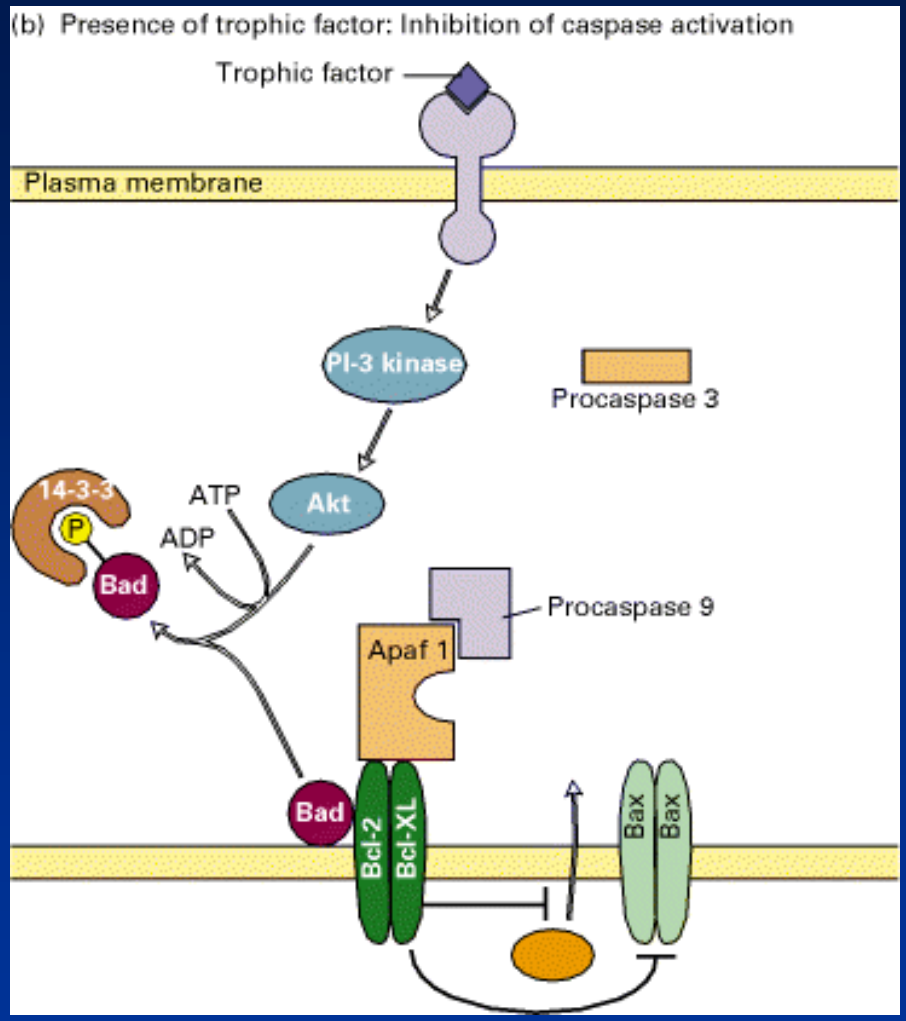
Such signals are mostly associated with the cell cycle, & is channeled through the pRb protein. e.g. TGF-β

Downregulation of/dysfunctional TGF-βR; Smad4 elimination; $p15^{INK4B}$ deletion; CDK4 unresponsive to INK4; pRb sequestration by E7;

Anti-differentiation - Myc

Evading Apoptosis





Limitless Replicative Potential

Hayflick's limit; senescence – crisis; hTERT; hTR

Sustained Angiogenesis

VEGF, FGFs; thrombospondin-1 (inhibitor); Proteases: bFGF in ECM (pro), plasmin to angiostatin (anti)

Tissue Invasion & Metastasis

E-cadherins; Integrins

The hallmarks just visited, show a cancer cell apart from its normal counterpart. These help us work towards effective drug targeting.

Metabolism can, the same way, provide a very useful distinction and metabolic profiles can give us a clearer picture about the genetic and expression changes that take place in a cancer cell – hence called a ‘hallmark’.

But…probably it is not really a cause but an effect of the other hallmarks…

That needs enquiry!

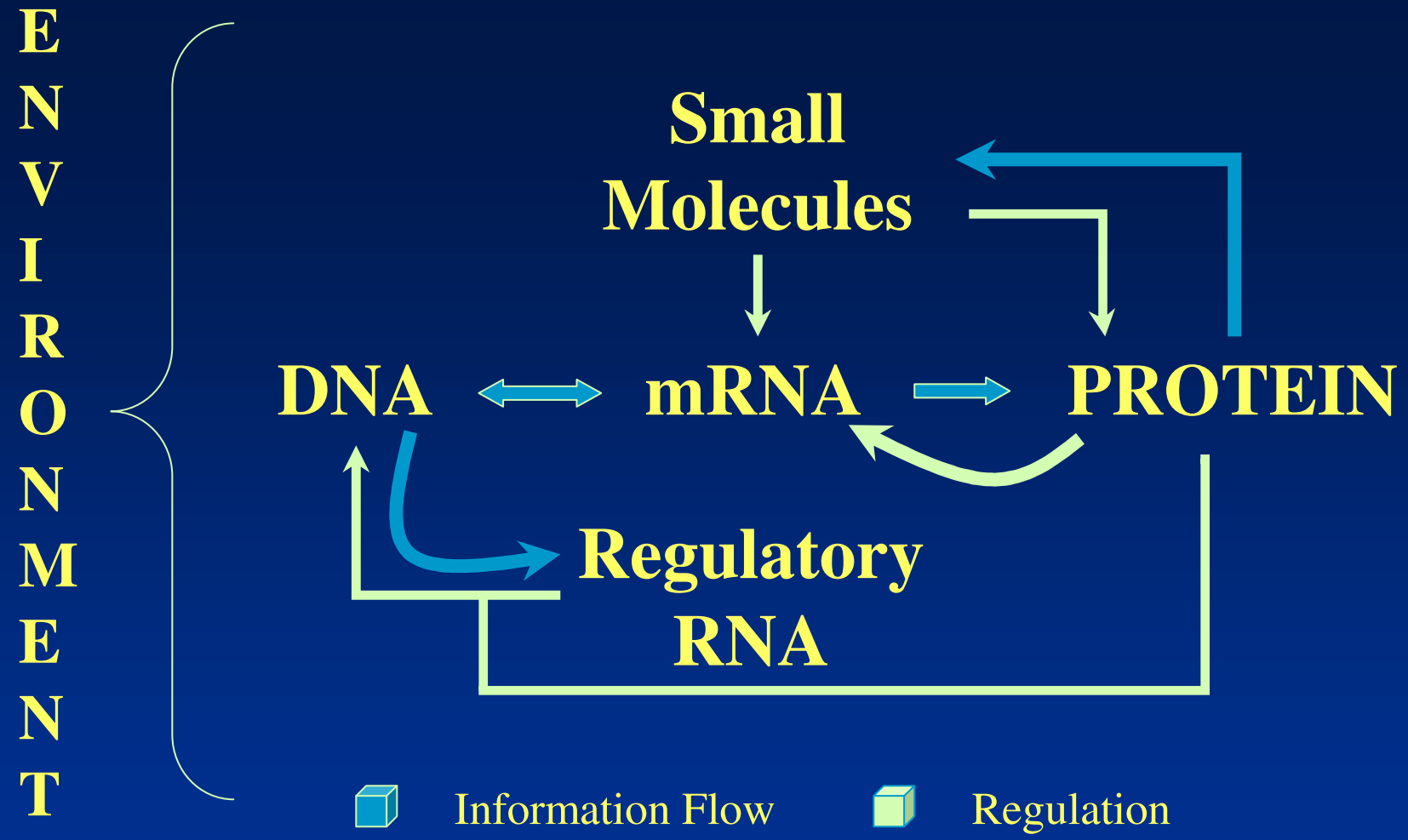
Metabolic Profile of Cancer

Metabolomics

The complete set of metabolites/low-molecular-weight intermediates, which are context dependent, varying according to the physiological, developmental or pathological state of the cell, tissue, organ or organism.

- Steve Oliver, Manchester University

The Bioenergetic status of the tumor



Measuring metabolite concentrations – more sensitive than following rates of chemical reactions.

Glycolysis & Lipid Metabolism have been studied.

The changes that occur in cancer cells in hypoxic regions of tumors have been monitored.

The effects of HIF-1β deficiency on tumor metabolism and growth were analyzed.

HIF-1 → Increased rate of glucose metabolism

HIF-1 → Induction of angiogenesis (VEGF)

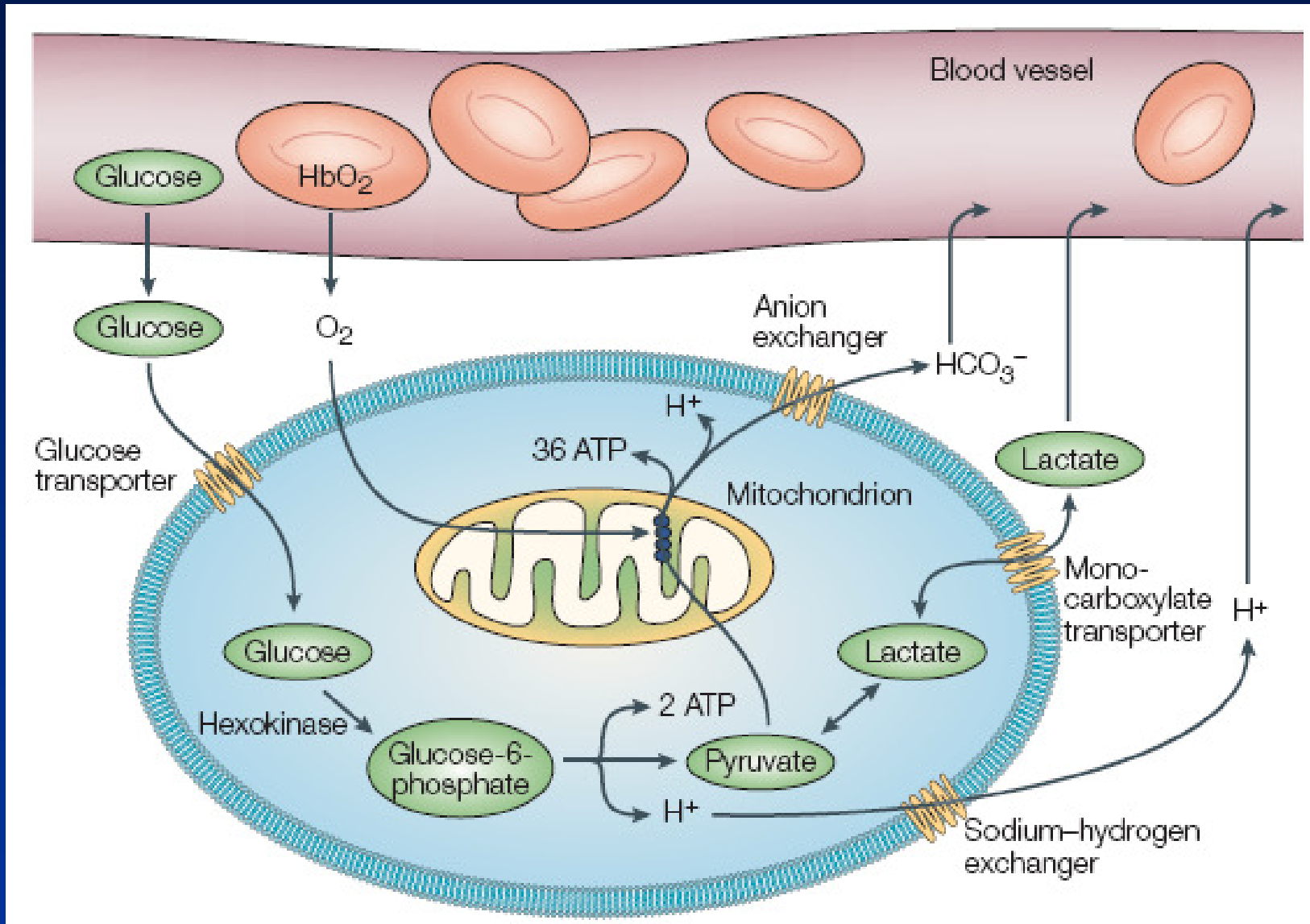
Warburg – 1920s

Propensity of cancer cells to utilize glucose and convert glucose to lactic acid even in the presence of oxygen – Aerobic glycolysis or the Warburg Effect.

This is probably due to:

- mitochondrial dysfunction
- oncogenic alterations
- adaptive response to the tumor microenvironment

Glucose metabolism in mammalian cells



Mitochondrial mutations

- VHL signals HIF-1 to degradation in the presence of O_2.
- Proline hydroxylation of HIF-1 (by PHD) necessary for its binding to VHL.
- PHD requires ketoglutarate and O_2 as substrates with the result of succinate (decreases PHD function) production.

- So, when enzymes that catabolize succinate or its products are decrease/mutated…

Adaptive responses

Hypoxia → Stabilization of HIF-1

↓ Transcriptional activation

Glucose transporters
Glycolytic enzymes (including LDH)
Angiogenic factors (VEGF)

Oncogenic alterations

Inactivation of VHL

Ras, HER2 signaling, PI3K

Myc (70% of cancers)

- glycolytic enzymes (HK2, ENO1 & LDH)
- glucose transporters

Akt (anti-apoptotic)

Advantages

Increased glycolysis suppresses ROS production by oxidative phosphorylation, which is implicated in senescence & apoptosis.

Might use mitochondria & O_2 for pyrimidine synthesis, rather than ATP synthesis – Coupling of nucleotide biosynthesis with mitochondrial machinery to achieve high proliferative rates.

Conclusion

Cancer *is* a systems disease that has risen out of genetic and metabolic adaptations, although more light has to be thrown on the latter. Amidst the heterogeneity & complexity, there seems to exist common themes.

Rigorous experimentation and modeling of the signaling *in the context of the metabolic state of the cell* will greatly improve our understanding the mechanisms of cancer.

Thank you!

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Janani for helping with a few topics & providing me with many papers.

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