Babylon Medical College
Clinical Biochemistry

Biochemistry of cancer

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Cancer

- Cancer is one of the most common diseases in the developed world:Cancer is not a single disease. It is caused by the uncontrolled growth of abnormal or mutated cells in the body, and cancer cells are characterized by their ability to rapidly grow and divide, and to undergo uncontrolled proliferation

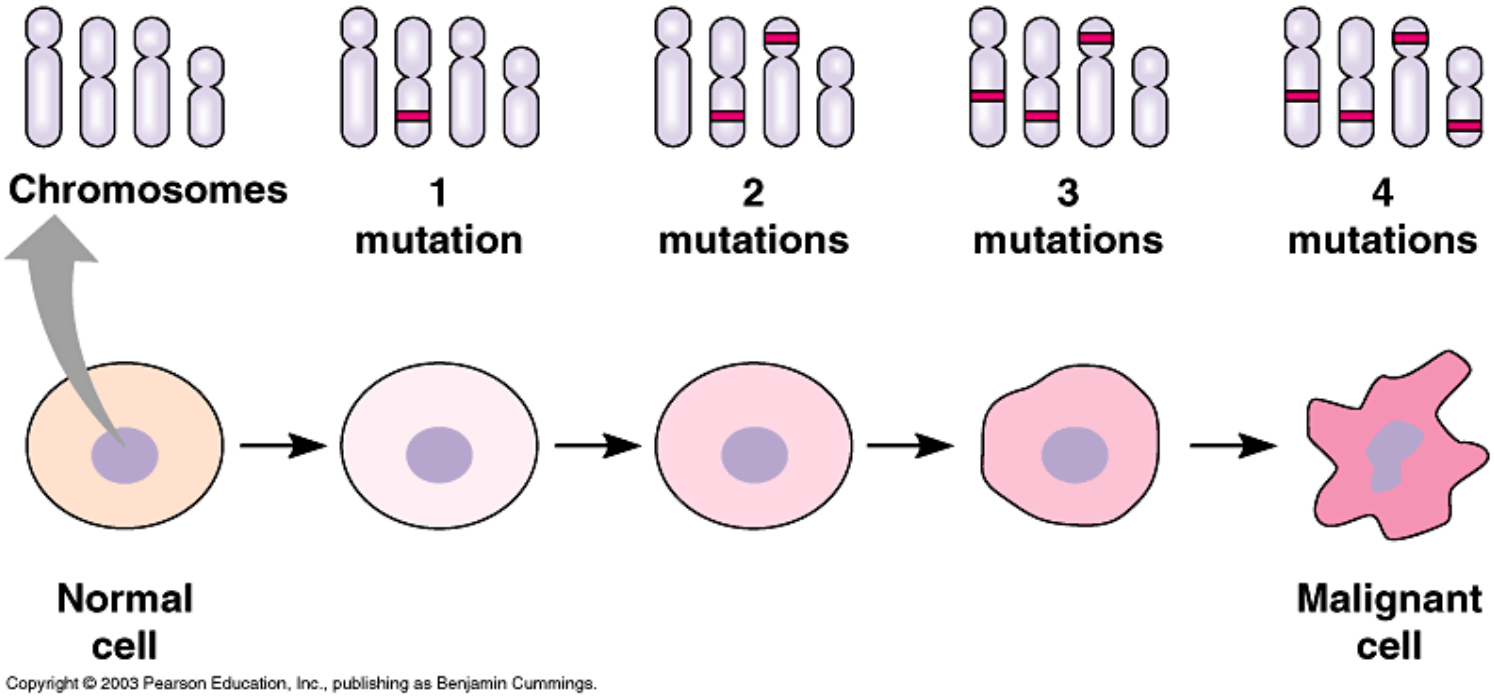
HOW DO TUMOURS DEVELOP?

- There has to be a change to DNA
- The change must cause an alteration in cell growth and behaviour
- The change must be non-lethal and be passed onto daughter cells

What causes cancer?

- Cancer arises from the mutation of a normal gene.
- Mutated genes that cause cancer are called oncogenes.
- It is thought that several mutations need to occur to give rise to cancer
- Cells that are old or not functioning properly normally self destruct and are replaced by new cells.
- However, cancerous cells do not self destruct and continue to divide rapidly producing millions of new cancerous cells.

How do normal cells become cancerous?



Selection within tumor for "most cancerous" cells

HOW DO TUMOURS DEVELOP?

- Alteration is to more than one gene
- Genes concerned are oncogenes and tumour suppressor genes
- Sequence of gene alterations from normal to benign to malignant
- Intrinsic and extrinsic / inheritance and environment key factors

- A factor which brings about a mutation is called a mutagen.
- A mutagen is mutagenic.
- Any agent that causes cancer is called a carcinogen and is described as carcinogenic.
- So some mutagens are carcinogenic.

Carcinogens

- Ionising radiation – X Rays, UV light
- Chemicals – tar from cigarettes
- Virus infection – papilloma virus can be responsible for cervical cancer.
- Hereditary predisposition – Some families are more susceptible to getting certain cancers. Remember *you can't inherit cancer* its just that you maybe more susceptible to getting it.

Occupational And Environmental Factors

- Asbestos
- Nickel
- Chromate
- Benzene
- Arsenic
- Radioactive substances
- Cool tars
- Herbicides/pesticides

Social And Psychological Factors

- Stress has been implicated in increased susceptibility to several types of cancers
- Sleep disturbances, diet, or a combination of factors may weaken the body's immune system

Chemicals In Foods

- Sodium nitrate when ingested forms a potential carcinogen, nitrosamine
- Sodium nitrate is still used because it is effective in preventing botulism
- Pesticide and herbicide residues

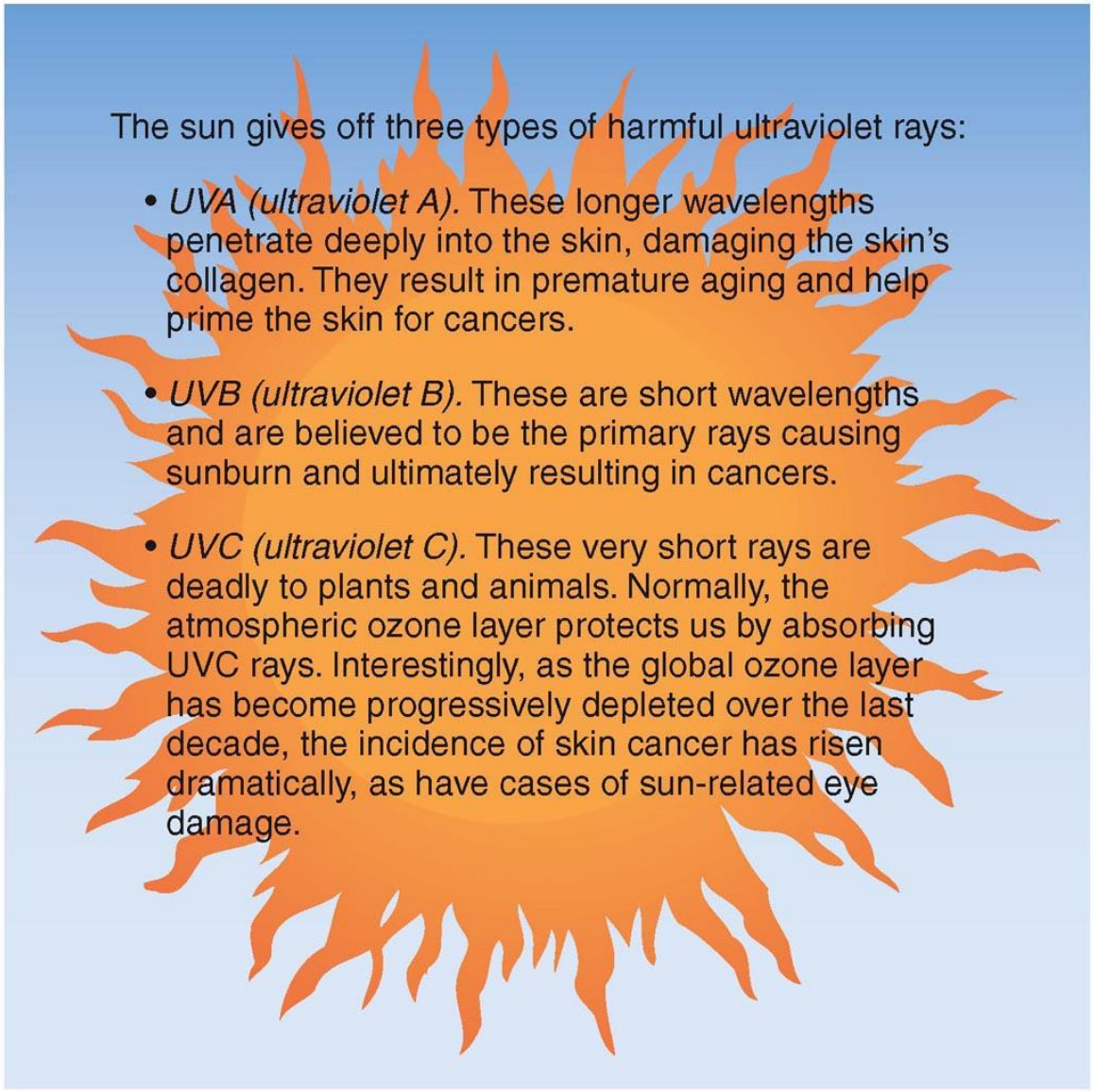
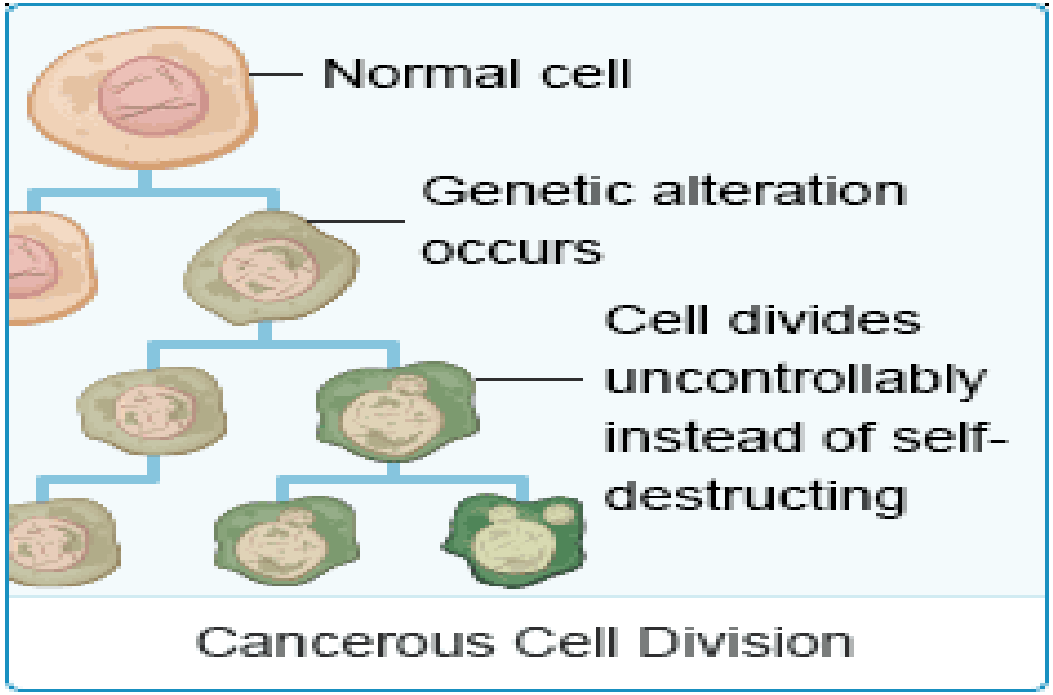

The sun gives off three types of harmful ultraviolet rays:
• *UVA (ultraviolet A).* These longer wavelengths penetrate deeply into the skin, damaging the skin's collagen. They result in premature aging and help prime the skin for cancers.
• *UVB (ultraviolet B).* These are short wavelengths and are believed to be the primary rays causing sunburn and ultimately resulting in cancers.
• *UVC (ultraviolet C).* These very short rays are deadly to plants and animals. Normally, the atmospheric ozone layer protects us by absorbing UVC rays. Interestingly, as the global ozone layer has become progressively depleted over the last decade, the incidence of skin cancer has risen dramatically, as have cases of sun-related eye damage.

Figure 16.7

Developing cancer cell



Four classes of genes are implicated in development of cancer:

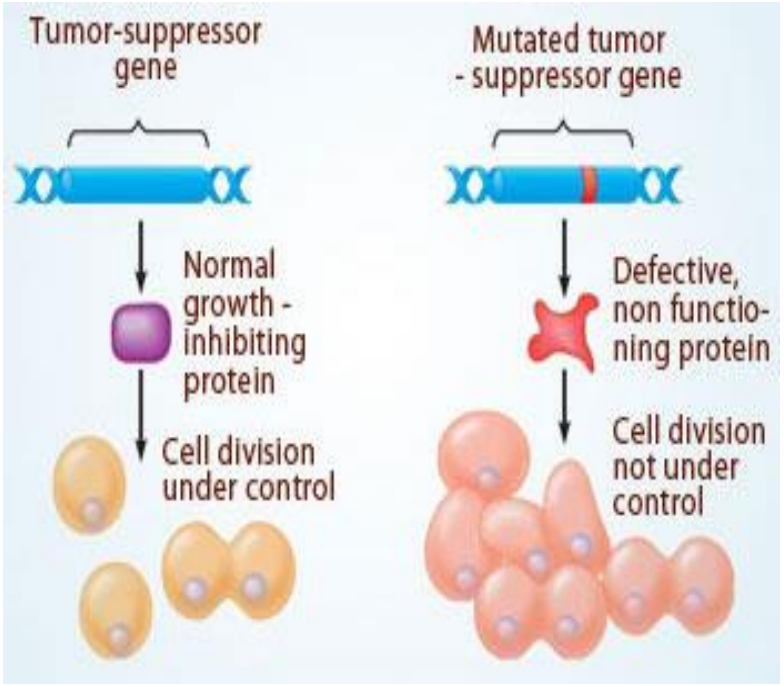
- 1) protooncogenes which are responsible for normal cell growth and differentiation (e.g. K-ras, N-ras).
- 2) tumor suppressor genes which are involved in recognition and repair of damaged DNA (e.g. P53 gene).
- 3) apoptosis-related genes are responsible for regulation of apoptosis.
- 4) DNA repair genes (e.g. BRCA1 and BRCA2).

Genes associated with cancer

Cancer Genes

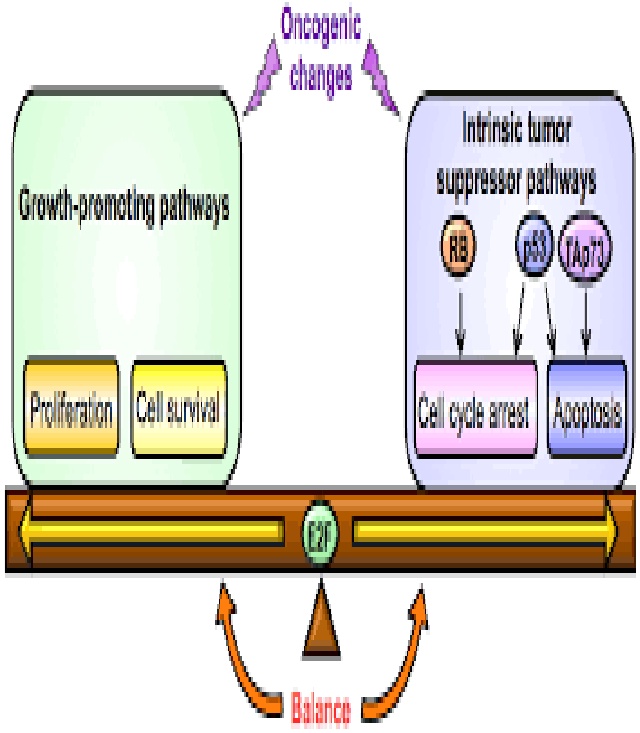
- **Proto-oncogenes** – normally promote normal cell growth; mutations convert them to oncogenes.
- **Tumor suppressor genes** – normally restrain cell growth; loss of function results in unregulated growth.
- **Mutator or DNA repair genes** – when faulty, result in an accumulated rate of mutations.

Oncogene and tumor suppressor gene mutation lead to cancer

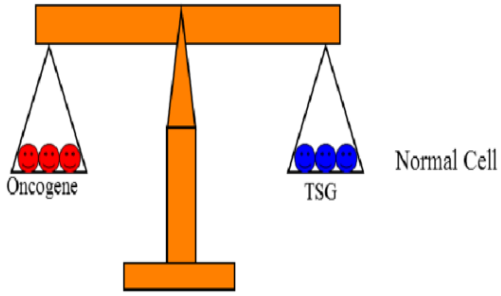


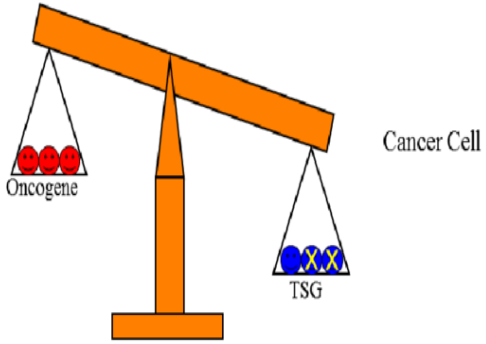
ONCOGENES

- **Oncogenes are mutated forms of cellular proto- oncogenes.**
- **Proto- oncogenes code for cellular proteins which regulate normal cell growth and differentiation.**

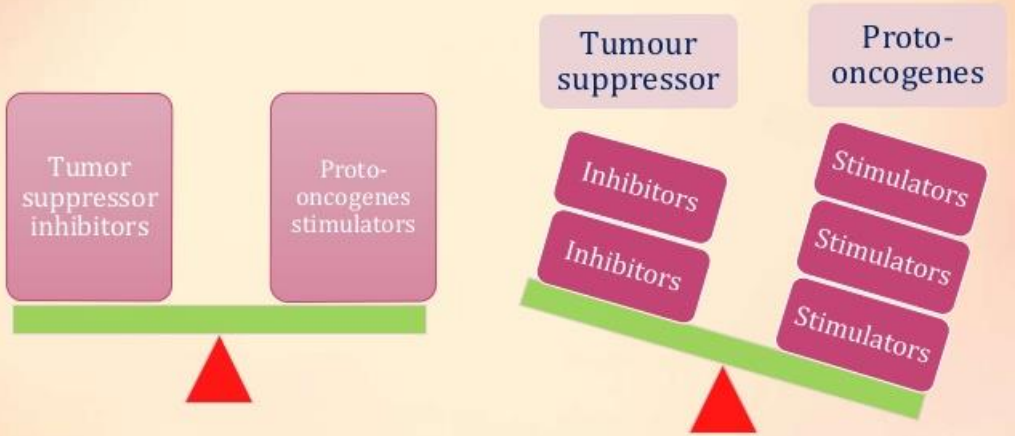


Functional balance/imbalance of Oncogene and Tumor suppressor gene (TSG) in normal and cancer Cells





Balance between factors stimulating and inhibiting cell growth



Action of Chemical Carcinogens

- Chemical carcinogens are usually ingested as **procarcinogens**. They are metabolised in the body, usually in liver, to become the active carcinogen. The enzymes responsible for the activation of procarcinogens are cytochrome P-450 system.

Mechanisms of action of chemical carcinogens are:

- (a) Carcinogens are generally electrophiles (molecules deficient in electrons); they readily attack nucleophilic (electron rich) groups of DNA.
- (b) Carcinogens may bind covalently to cellular DNA.
- (c) These changes will lead to DNA alterations, in spite of DNA repair, with increased probability of mutations.

Chemical carcinogens may produce the cancer

- (a) At the site of exposure, e.g. buccal cancer in tobacco chewers, skin cancer in tar workers.
- (b) At the site of metabolism, e.g. liver cancer produced by aflatoxin.
- (c) At the site of elimination, e.g. bladder cancer in persons working with aromatic dyes.

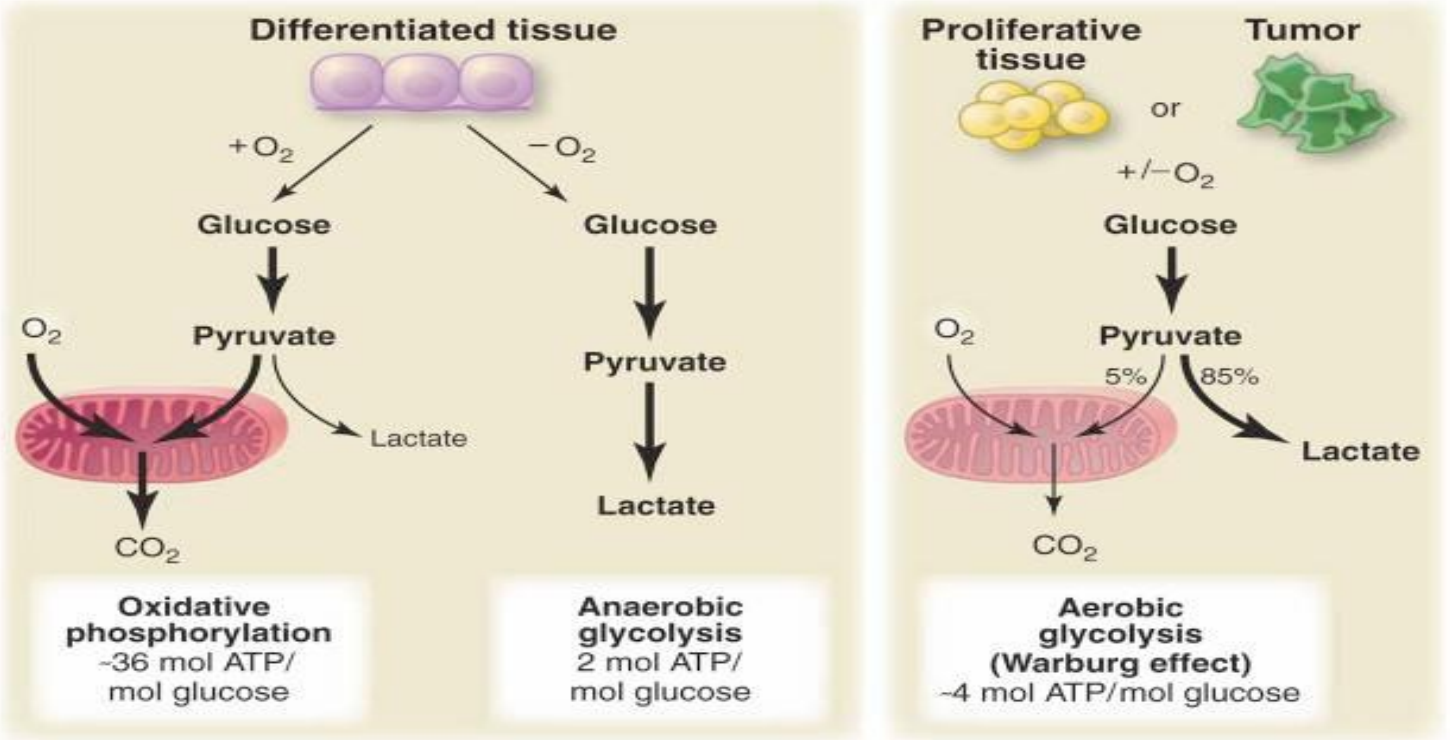
Metabolism in cancer cell

Cancer cell depend on Glycolytic for generation of ATP in addition in generating many glycolytic intermediates that are precursors to anabolic processes such as pentose phosphate pathway generating NADPH, ribose-6-phosphate, amino acid, lipids, and other cellular sources of energy (*de novo* syntheses of carbohydrates, proteins, and fats)

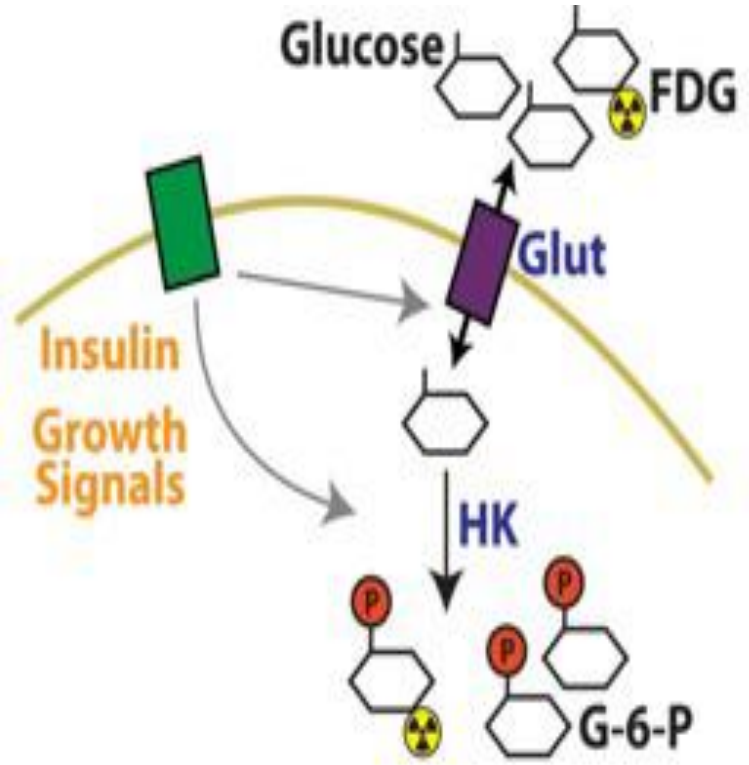
GLYCOLYSIS AND RESPIRATION IN CANCER CELLS

- Glycolysis can be activated by an increase in the concentration of fructose 2,6-bisphosphate which activates the rate-limiting enzyme phosphofructokinase 1.
- Fructose 2,6-bisphosphate is produced by the bifunctional enzyme phosphofructokinase 2/ fructose 2,6-bisphosphatase (PFKFB).
- The inducible PFKFB3 isozyme is constitutively expressed by many tumor cells.

TumorMetabolism: How is it Different ?



- Cancer cells must compensate for the ~18-fold lower efficiency of ATP production
- afforded by glycolysis relative to mitochondrial oxidative phosphorylation
- Cancer cells upregulate glucose transporters, which substantially increases glucose
- import into the cytoplasm



Table(1) Molecular Correlation Concept and Affected Processes

Biochemical Process	***Alteration in Cancer Cells***
Pyrimidine and purine synthesis	*Increased*
Pyrimidine and purine catabolism	*Decreased*
RNA and DNA synthesis	*Increased*
Glucose catabolism	*Increased*
Glucose synthesis	*Decreased*
Amino acid catabolism (for gluconeogenesis)	*Decreased*
Urea cycle	*Decreased*

Cancer prevention

avoid Tobacco smoking and **Alcohol use**

Dietary modification is another important approach to cancer control. There is a link between overweight and obesity to many types of cancer

Diets high in fruits and vegetables may have an independent protective effect against many cancers. Regular physical activity and the maintenance of a healthy body weight, along with a healthy diet, considerably reduce cancer risk.

control Pollution of air, water and soil with carcinogenic chemicals contributes to the cancer

control exposure circumstances in the working environment are carcinogenic to humans and are classified as occupational carcinogens.

Cancer Detection and Diagnosis

We will see in next class...