GLUCOSE HOMEOSTASIS – I: Brief Review of: AEROBIC METABOLISM, ELECTRON TRANSPORT CHAIN & ANAEROBIC METABOLISM

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Energy metabolism with emphasis on Glycolysis

What is Glycolysis?

- Glycolysis is a:
  - Major metabolic pathway for Energy production via degradation of Glucose and other Monosaccharides;
- Unique pathway because it can occur:
  - In the presence of O_2 (Aerobic Glycolysis) in cells that contain mitochondria;
  - In the absence of O_2 (Anaerobic Glycolysis), and in cells that do not contain mitochondria, or
- **Fig. 1:** Outline of Glycolysis:

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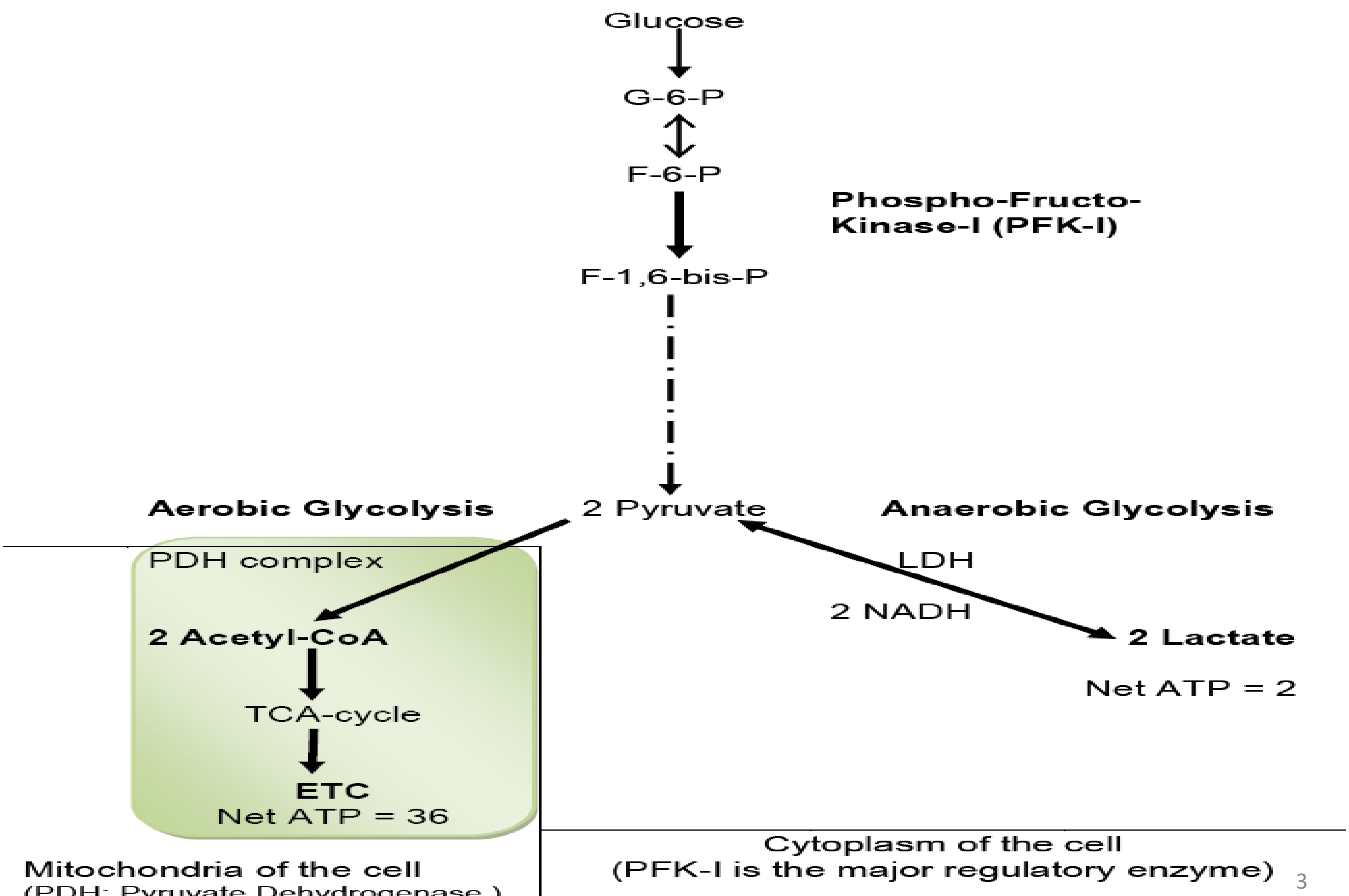


How is ATP produced during Aerobic metabolism?

- Pyruvate is the end product of Aerobic Glycolysis,
- Pyruvate is converted to Acetyl-CoA, which then enters the TCA-cycle in the Mitochondria;
- Reducing Equivalents from TCA-cycle enters Electron Transport Chain (ETC);
- Mitochondria is the power house of the cell,
- Cells use Proton-Pumping System made up of proteins inside Mitochondria to generate ATP;
- Synthesis of ATP is coupled with Oxidation of NADH and reduction of Oxygen in ETC,
- Process is known as Oxidative Phosphorylation;

- Process involved 3 key steps:
    - Transfer of electrons from NADH via Electron carriers to Oxygen,
    - Transfer of electrons by carriers generates Proton (H^+) Gradient across Inner Mitochondrial membrane;
    - ATP is synthesized when H^+ spontaneously diffuses back across the Inner Mitochondrial membrane;

- ATP Synthetase converts the Free Energy of the Proton Gradient to Chemical Energy in the form of ATP;

What is the Electron Transport Chain (ETC)?

- Electron Transport (Respiration) Chain (ETC) is the Final Common Pathway in Aerobic cells,
- In ETC electrons derived from various substrates are transferred to Oxygen;
- ETC is composed of a series of highly organized Oxidation-Reduction Enzymes whose reactions can be represented by:

Reduced A + Oxidized B ←==→ Oxidized A + Reduced B

Where is ETC located in the cell?

- ETC is located in the Inner membrane in the Mitochondria,

- Enzymes of the ETC are embedded in the inner membrane in association with the enzymes of Oxidative Phosphorylation;

What are Reducing Equivalents?

- Reducing Equivalents are sources of electrons for ETC,
- Two major Reducing Equivalents:
- **$NADH+H^+$** : Reduced Nicotinaminde-Adenine Dinucleotide
  - It produces 3 molecules of ATP in ETC;
- **$FADH_2$** : Reduced Flavin-Adenine Dinucleotide,
  - It produces 2 molecules of ATP in ETC;
- Other reducing equivalents are:
  - **$NADPH + H^+$;**
  - **$FMNH_2$**;

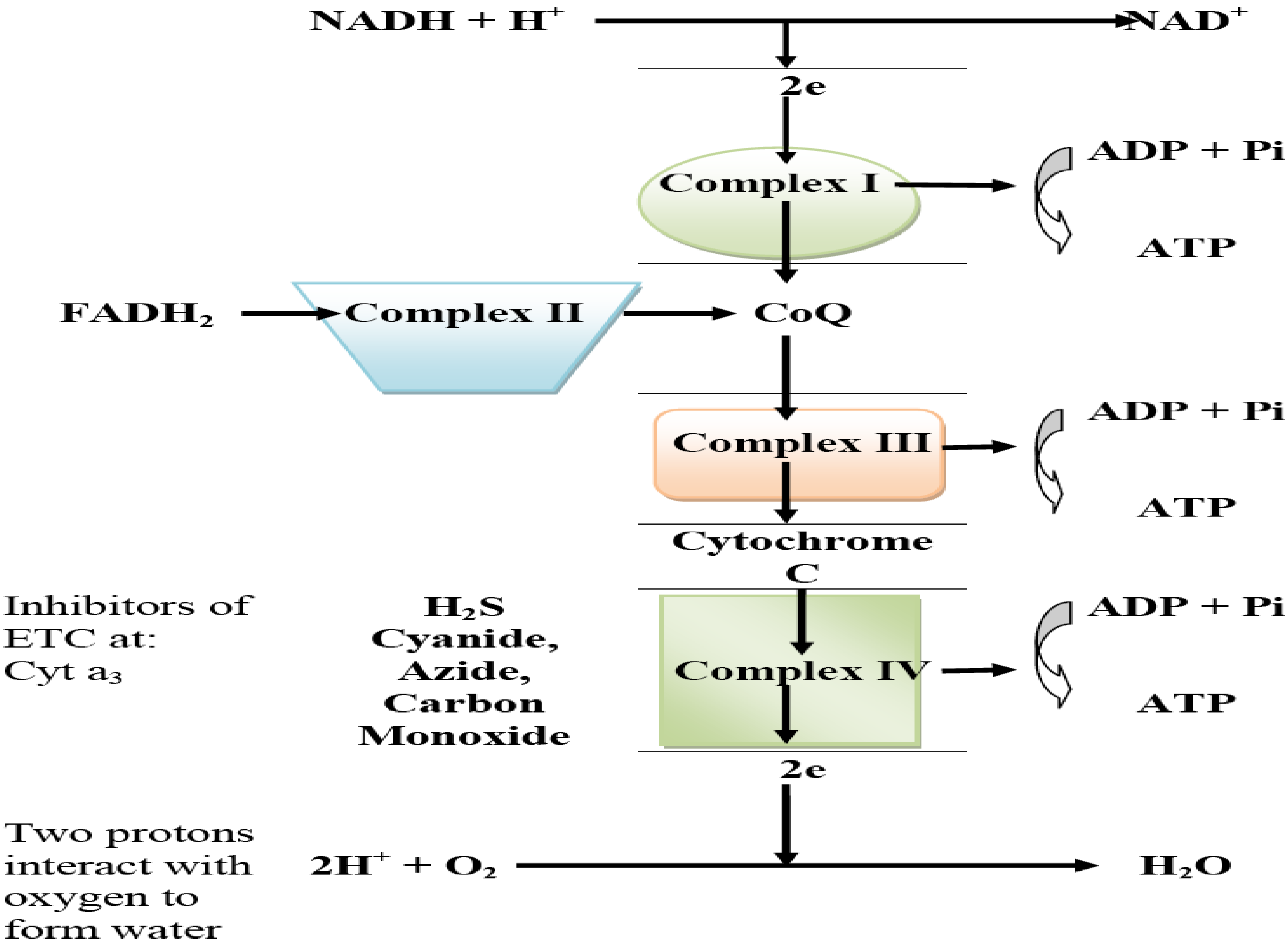
What are the major components of the ETC?

- ETC is made up of Four Major Complexes:
- **Complex I**:
  - NADH, Coenzyme Q Reductase,
  - Point of entry into ETC for electrons from NADH
- **Complex II**:
  - Succinate, Coenzyme Q Reductase,
  - Point of entry into ETC for electrons from Succinate;

- **Complex III**:
    - Coenzyme Q, Cytochrome C Reductase,
    - Electron acceptor for Coenzyme Q;
- **Complex IV**:
    - Cytochrome C Oxidase,
    - Electron acceptor for Cytochrome C
    - Cytochrome **a a_3**

Fig 2: Simplified schematic diagram of ETC,

Fig. 2: Schematic diagram of ETC: showing the complexes, points of formation of ATP and point of action of Inhibitors of ETC



What do you understand by Oxidative Phosphorylation?

- It is main source of energy in Aerobic metabolism
- Process by which Free Energy released when electrons are transferred along the ETC is coupled to the formation of ATP from ADP and Pi

ADP + Pi + Energy ==========➔ ATP

- Two possibilities must be considered:
- **Intact Mitochondria**:
  - Transport of Electrons and Oxidative Phosphorylation of ADP are tightly Coupled reactions,
  - Free Energy released is stored as ATP,

- **Damaged Mitochondria**:
  - Electron transport may occur without Oxidative Phosphorylation,
  - Free Energy released as Electrons are transported will not be stored as ATP but will instead be lost as heat,

What are some effects of prolonged Anaerobic Glycolysis?

- Anaerobic Glycolysis leads to production of:
  - Two molecules of Lactic Acid (Lactate);
  - Total of 4 ATP,
  - Net of 2 ATP per molecule of Glucose,
- Summary of equation for Anaerobic Glycolysis:
- (All enzymes are present in Cytosol)

Glucose + 2ADP + 2P ===➔ 2 Lactate + 2 ATP + 2H^{+}

- End product of Anaerobic Glycolysis is Lactate;

- Prolonged Anaerobic Glycolysis causes Lactic Acidosis;
- Muscles become Tired and Sore;
- Lungs respond by Hyperventilation, blowing out CO_2, which helps to reduce accumulation of acid in the cells and restore Acid – Base balance;
- Lactic acid is removed via Cori Cycle in the Liver;

What is the relationship between Intracellular pH and Anaerobic Glycolysis?

- To answer this question one need to know the Glycolytic reaction catalyzed by **Phosphofructokinase-1 (PFK-I)**

  Fructose-6-P + ATP ==➔ Fructose 1,6-bisphosphate + ADP

- It is the Rate-limiting Enzyme and important Regulatory Site of Glycolysis;
- Reaction is Irreversible under Intracellular Conditions;
- Important **Negative Allosteric Effectors** of **PFK-I** are:
  - **Hydrogen ions (Low pH),**
  - **Citrate,**
  - **ATP**,

- Important **Positive Allosteric Effectors of PFK-I** are:
  - **AMP,**
  - **Fructose 2,6-bisphosphate,**
  - **Inorganic Phosphate (P_i);**

- Under Anaerobic conditions:
  - End product of Glycolysis is Lactic acid;
  - Cells must dispose of Lactic Acid so as to prevent its accumulation;
  - Excessive Glycolysis in tissues lower blood pH causing Lactic acidosis;

- Cell membrane contains Symport mechanism for the transportation of Lactate and H^+ out into the blood,
  - Regulatory mechanism that prevents accumulation of Lactate and H^+ ions in cells, preventing lowering of pH in cells;
- **Inhibition of PFK-I by H^+ ions** is part of this mechanism;
  - Thus, H^+ ions are able to shut off Glycolysis, the process responsible for decreasing the pH in cells;
- Removal of Lactic acid in cells requires that blood is available to carry it away to the liver;

- When blood flow is inadequate: Example:
  - Heavy Exercise of Skeletal Muscle, or
  - An Attack of Angina Pectoris in case of the Heart,
- The H^+ ions cannot escape from the cells fast enough,
- **The need for ATP within the cells, because of lack of Oxygen, may partially over-ride the Allosteric Inhibition of PFK-I by H^+ ions**;
- Anaerobic Glycolysis will proceed causing accumulation of H^+ ions and Lactate in the cells, resulting in pain;

- In the Skeletal Muscle:
- Pain sensation can be removed by terminating exercise; thus allowing for removal of the excess Lactic acid from the muscle cells via Cori cycle;

- Heart (Angina Pectoris):
- Rest or Pharmacological agents that increase blood flow or decrease the need for ATP within the cardiac cells may be effective;

Why are cancer cells called "Metabolic Parasites"?

- In the presence of O_2 cancer cells convert Glucose to Lactate, which is then released in blood, picked up by the Liver for conversion to Glucose via Gluconeogenesis;
- Conversion of Lactate to Glucose in Liver requires **6 ATP**;
- Cancer cells produce net of **2 ATP** per molecule of Glucose converted into Lactate in Glycolysis;
- Thus, Liver needs to provide an extra **4 ATP**, to convert the Lactate to Glucose;
- Therefore, Cancer cells can be looked upon as Metabolic Parasite that depends on the Liver for a substantial part of its energy;

- Large masses of cancer cells can be a considerable metabolic drain on the host organism, in addition to causing other local and systemic problems;
- **Cancer cells are Metabolic Parasites because**:
  - They utilize abnormally large amounts of Glucose, which in the presence of Oxygen, are convert into Lactate that is release in the blood;
  - Lactate is converted to Glucose via Gluconeogenesis in liver at a large net cost to ATP stores in the body;

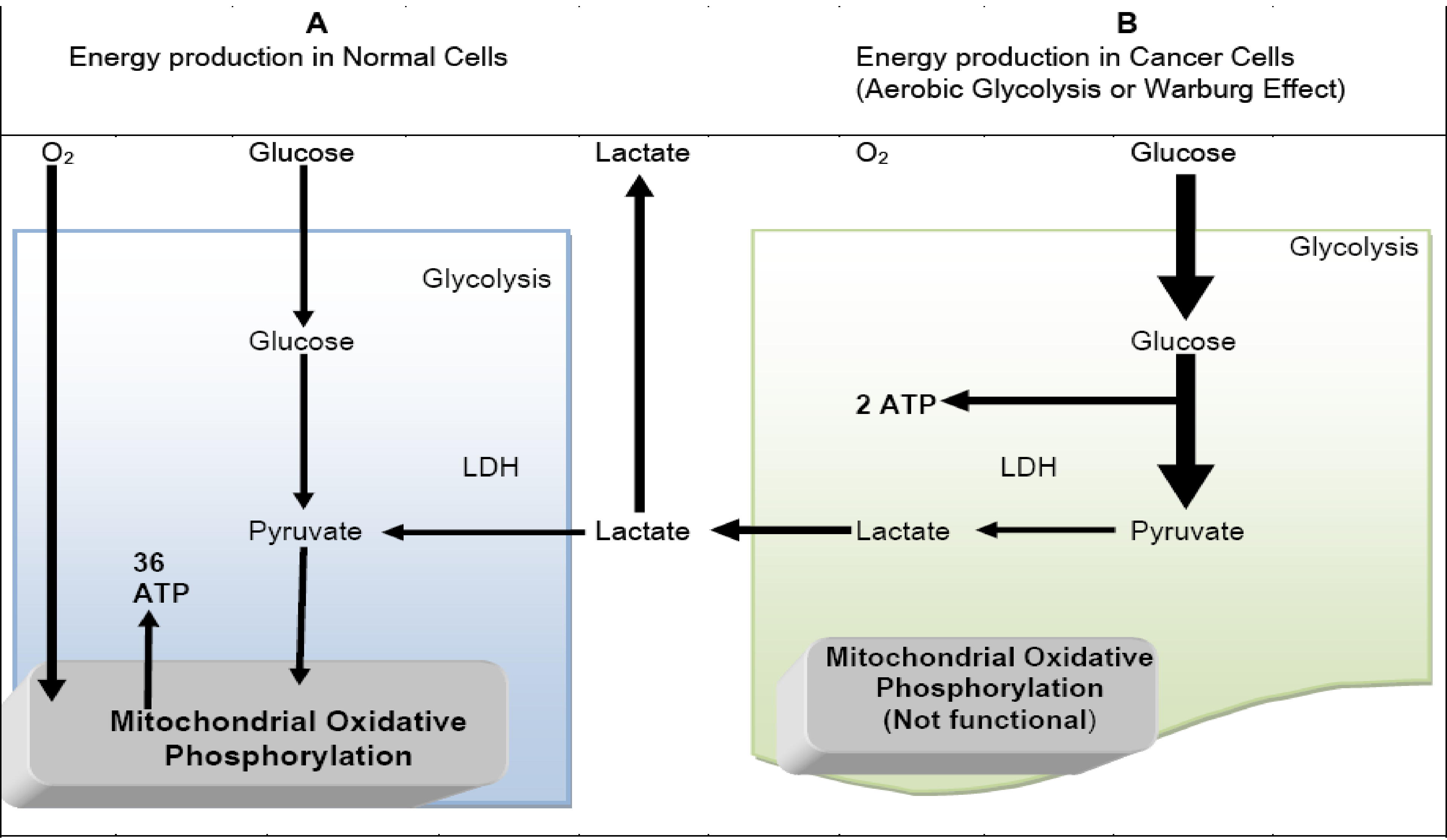
What is Pasteur Effect?

- **Pasteur Effect** states that:
- Rate of Glycolysis is significantly reduced in the presence of Oxygen;

What is Warburg Effect?

- **Warburg Effect (Aerobic Glycolysis)** states:
- In cancer cells, availability of oxygen does not affect the rate of Glycolysis;
- In the presence of Oxygen normal cells utilize Oxidative Phosphorylation in mitochondria to generate energy,
- In the presence of Oxygen cancer cells utilize large amount of Glucose to generate energy via Glycolysis, and makes less use of Oxidative Phosphorylation in the mitochondria;
- **Fig. 3: Simple diagram to illustrate Warburg Effect**

Fig. 3:
Normal cells (**A**): Oxidative Phosphorylation for energy; net 36 ATP per Glucose; Cancer cells (**B**): Glucose to Lactate in presence of Oxygen (Aerobic Glycolysis or Warburg Effect), to generate net of 2 ATP per Glucose



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