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

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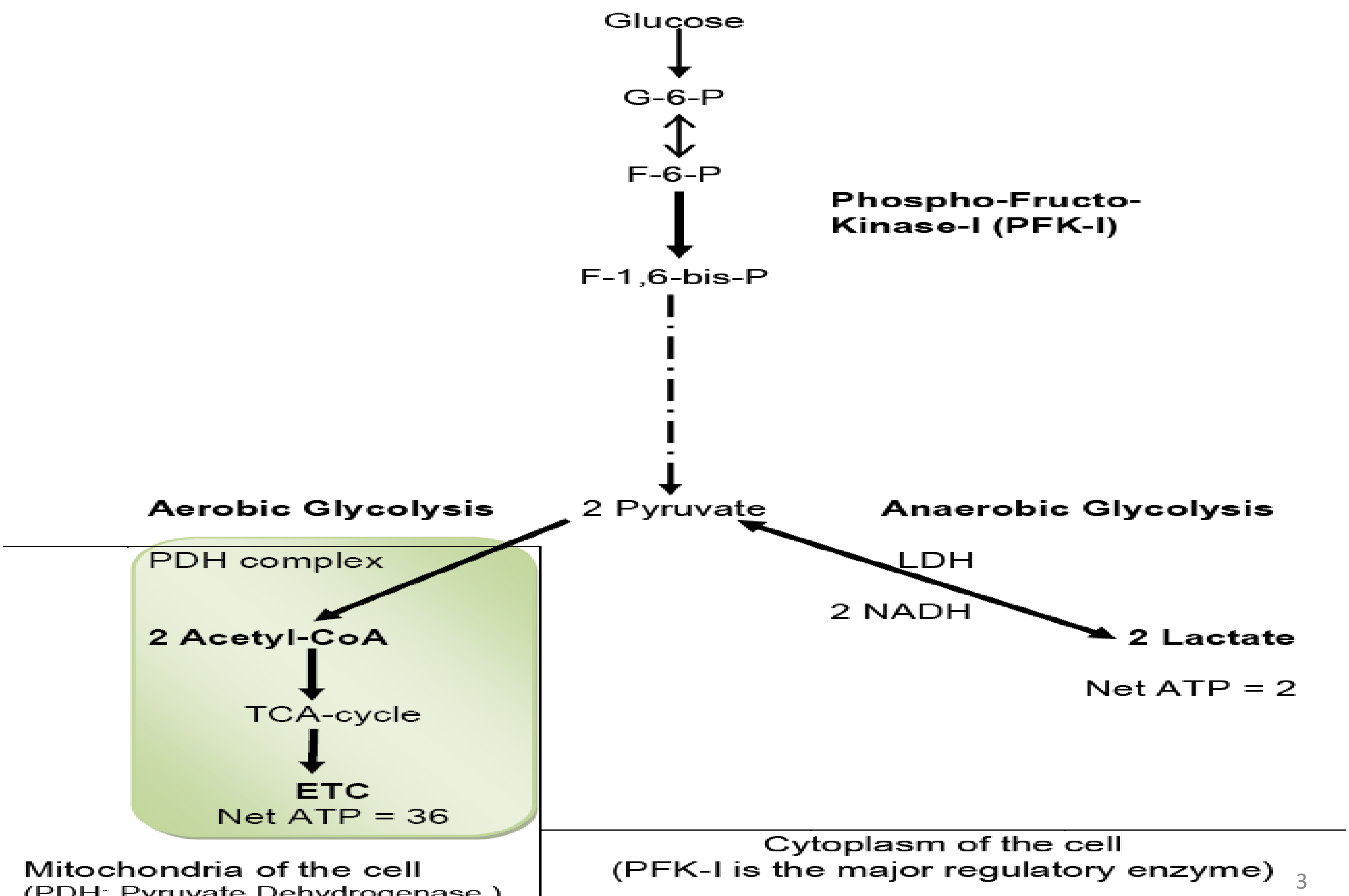
Glycolysis

What is Glycolysis?

- Metabolic pathway for production energy via degradation of Glucose and other Monosaccharides;
- It can occur:
  - In presence of O_2 (Aerobic Glycolysis) in cells with mitochondria;
  - In the absence of O_2 (Anaerobic Glycolysis) in cells that do not contain mitochondria;
- **Fig. 1:** Basics in Glycolysis: Aerobic & Anaerobic

Fig. 1: Basics in Glycolysis



How is ATP produced during Aerobic metabolism?

3 major pathways involved:

Glycolysis ===➔ TCA cycle ===➔ ETC ===➔ ATP

- **Pyruvate** is end product of **Aerobic Glycolysis**,
- **Pyruvate** is converted to **Acetyl-CoA**, which then enters **TCA-cycle** in 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 called Oxidative Phosphorylation**;

- **Oxidative Phosphorylation involves 3 Key steps**:
  - **Transfer of electrons in NADH via ETC to Oxygen,**
  - **Transfer of electrons by carriers in ETC generates Proton (H^+) Gradient across Inner Mitochondrial membrane;**
  - **ATP is synthesized when H^+ spontaneously diffuses back across the Inner Mitochondrial membrane;**
- **ATP Synthetase converts Free Energy of Proton Gradient to Chemical Energy in the form of ATP**;

What are Reducing Equivalents?

- They are sources of electrons used in ETC;
- **Two major Reducing Equivalents**:
  - **$NADH+H^+$** : Reduced Nicotinaminde-Adenine Dinucleotide
    - **$NADH+H^+$** produces **3 ATP in ETC**;
  - **NAD is the biologically active form of Vit B-3 (Niacin or Nicotinamide)**

- **$FADH_2$** : Reduced Flavin-Adenine Dinucleotide
  - It produces **2 ATP in ETC**;

  - **FAD is biologically active form of Vit B-2 (Flavin)**
- **Other reducing equivalents are**:
  - **$NADPH + H^+$;**
  - **$FMNH_2$**;

What is Electron Transport Chain (ETC)?

- **Electron Transport (Respiration) Chain (ETC) is the Final Common Pathway in Aerobic metabolism,**
- In ETC electrons derived from various substrates are transferred to Oxygen;
- ETC is composed of several 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 **Inner Mitochondrial membrane**

- ETC Enzymes are embedded in Inner membrane of the mitochondria in association with enzymes involved in Oxidative Phosphorylation;

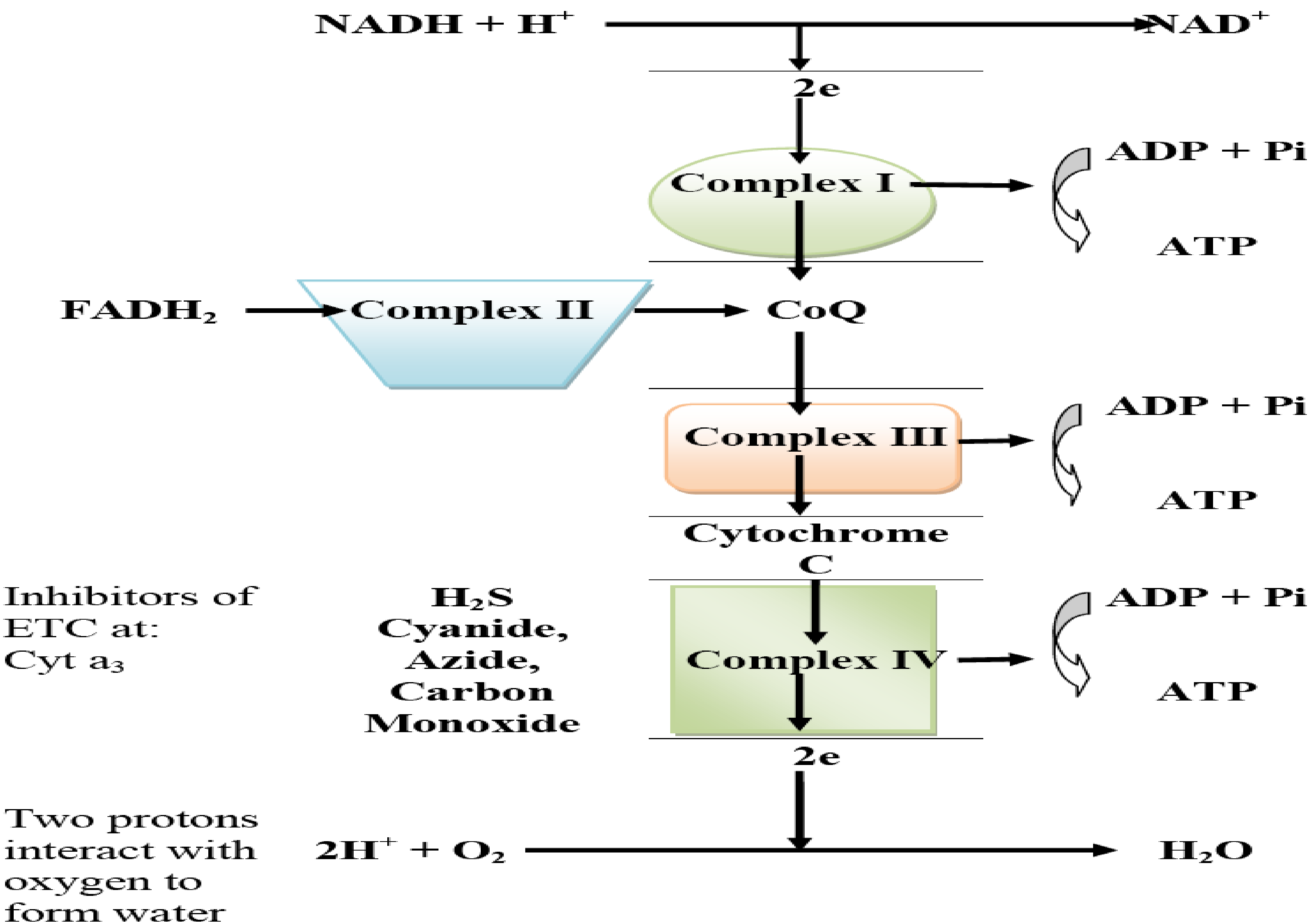
What are the major components of the ETC?

- ETC is made up of **Four Major Complexes**:
- **Complex I**:
  - **NADH, Coenzyme Q Reductase**,
  - Point of entry in ETC for electrons from **NADH**;
- **Complex II**:
  - **Succinate, Coenzyme Q Reductase,**
  - Point of entry in 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 $\mathbf{a}\ \mathbf{a_3}$

Fig 2: Simplified schematic diagram of ETC,

Fig. 2: Schematic diagram of ETC: showing 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 is released **BUT** is not stored as ATP; **it is lost as heat**;
  - **Process is referred to as uncoupling of ETC from Oxidative Phosphorylation**;

What are some effects of prolonged Anaerobic Glycolysis?

Anaerobic Glycolysis: One molecule of Glucose gives:

- **2 Lactic Acid** (Lactate);
- **Total of 4 ATP**,
- **Net of 2 ATP**,

- 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;

$$CO_2 + H_2O \Longleftrightarrow H_2CO_3 \Longleftrightarrow H^+ + HCO_3^-$$

- Lactic acid is removed via Cori Cycle in Liver;

What is the relationship between Intracellular pH and Anaerobic Glycolysis?

- Need to know the Glycolytic reaction catalyzed by **Phosphofructokinase-1 (PFK-1)**

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

  - Rate-limiting Enzyme and important Regulatory Site of Glycolysis;
  - Reaction is Irreversible under Intracellular Conditions;

- Important **Negative Allosteric Effectors** of **PFK-1** are:
  - **High [H^+] or Low pH,**
  - **Citrate,**
  - **ATP**,
- Under Anaerobic conditions:
  - End product of Glycolysis is **Lactic acid**;
  - Cells **must** dispose of **Lactic Acid** to prevent its accumulation;

- Cell membrane has **Symport mechanism** for the transportation of Lactate & H^+ out into blood,
  - **Major regulatory mechanism that prevents accumulation of Lactate & H^+ in cells, thus preventing lowering of pH in cells;**

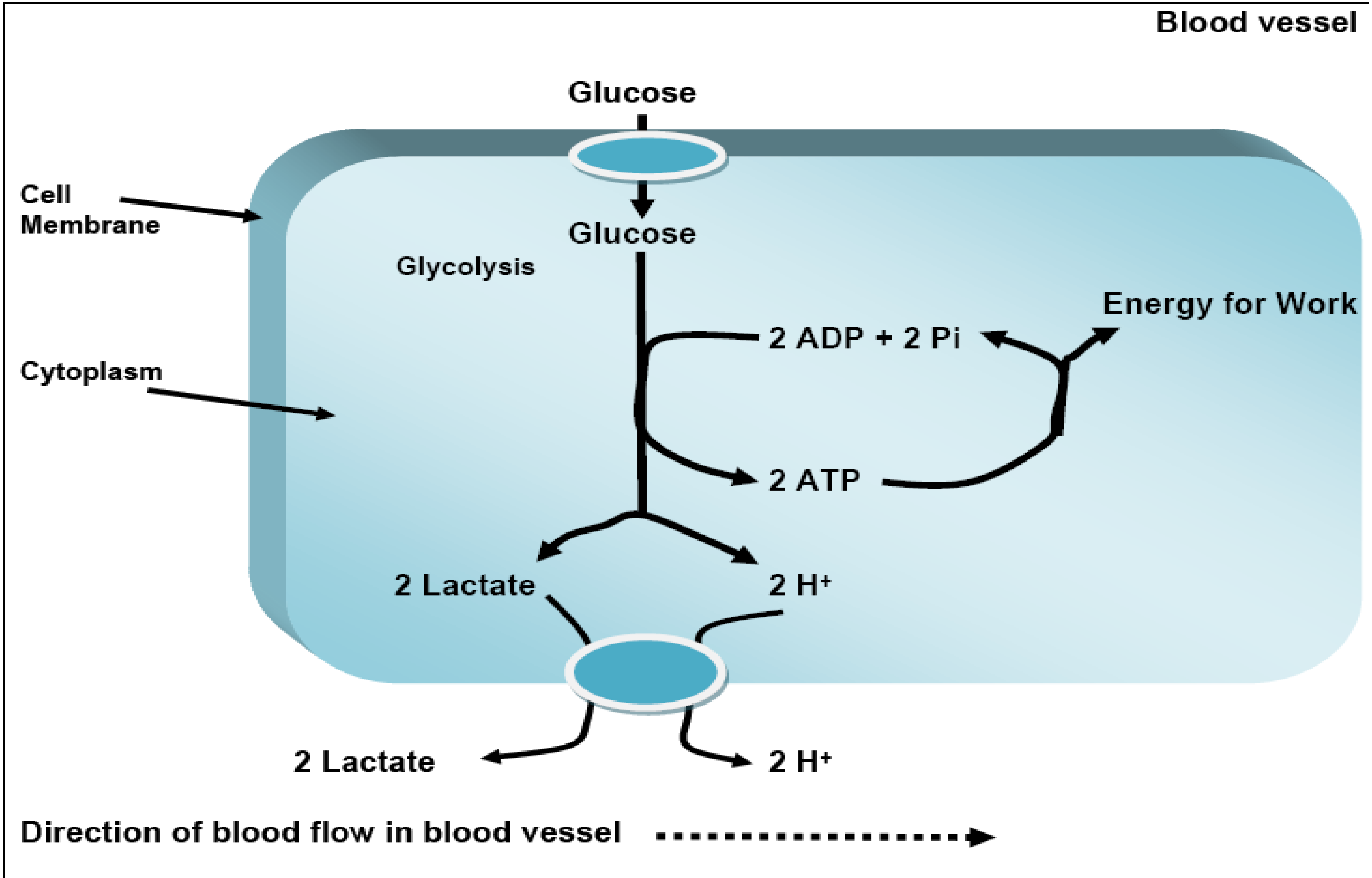
- **Inhibition of PFK-I by [H^+]** is part of mechanism;
  - Thus, [**H^+]** can inhibit Glycolysis, the process that is responsible for decreasing pH in cells;
- **Removal of Lactic acid in cells requires that blood is available to carry it away to the liver**;

- **When blood flow is inadequate**: For Example:
  - Heavy Exercise of Skeletal Muscle, or
  - An Attack of Angina Pectoris,
- **H^+ ions cannot escape from cells fast enough**,
  - **The need for ATP within the cells, because of lack of Oxygen, may partially over-ride the Allosteric Inhibition of PFK-1 by H^+ ions**;
- **Anaerobic Glycolysis proceed causing accumulation of H^+ ions and Lactate in the cells, resulting in pain;**
- **Fig. 3**

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

Fig 3: **Regulation of Anaerobic Glycolysis in cell: Symport action for removal of Lactic Acid in the cell**



Why are cancer cells called "Metabolic Parasites"?

- In 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 requires **6 ATP**;
- Cancer cells produce **Net of 2 ATP** per 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;**
- Cancer cells can be considerable metabolic drain on 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 blood;
  - Lactate is converted to Glucose via Gluconeogenesis in liver at a large net cost to ATP stores in the body;

Pasteur Effect and Warburg Effect

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

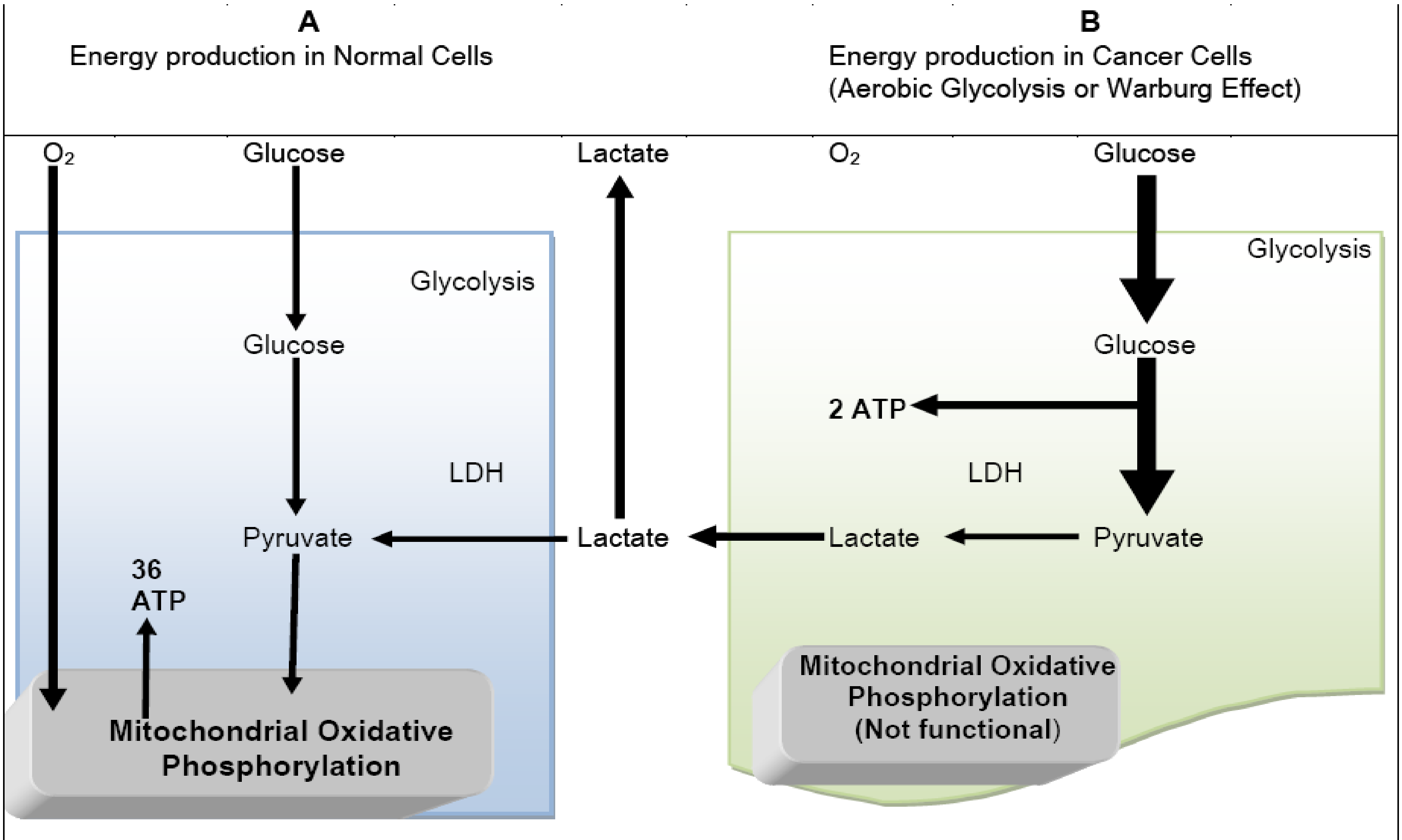
- **Warburg Effect (Aerobic Glycolysis)** states:
  - **In cancer cells, availability of Oxygen does not affect the rate of Glycolysis;**

What is Warburg Effect?

- In the presence of Oxygen **cells** usually 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



REFERENCES

- Textbook of Biochemistry, with clinical correlations, Ed. By T. M. Devlin, 4th Ed.
- Harper's Illustrated Biochemistry 26th Edition; 2003; Ed. By R. K. Murray et. al.
- Biochemistry, By V. L. Davidson & D. B. Sittman. 3rd Edition.
- Hames BD, Hooper NM, JD Houghton; Instant Notes in Biochemistry, Bios Scientific Pub, Springer; UK.
- VJ Temple Biochemistry 1001: Review and Viva Voce Questions and Answers Approach; Sterling Publishers Private Limited, 2012, New Delhi-110 – 020.
- M. Lopez-Lazaro; The Warburg Effect: Why and How do cancer cells activate Glycolysis in the presence of Oxygen? Anti-cancer agent in Medicinal Chemistry, 2008, Vol 8, No. 3, 305 – 312
- WWW.zonehome.com/met/metglucose.html
- WWW.niko.unl.edu/bs101/notes/lecture12.html