F214 Communication, homeostasis and energy

Unit 4: Respiration

ATP

The process of **respiration** releases energy from food molecules, mainly glucose. Energy is released in the form of **ATP** (adenosine triphosphate), a molecule which is often described as the universal energy currency of cells, because it can be used to fuel all metabolic reactions which require energy and is immediately available wherever there is ATP. It is formed from one molecule of **ADP** (adenosine diphosphate) and one extra inorganic phosphate group (Pi)

Aerobic respiration takes place under aerobic conditions – where oxygen is present – and has a higher overall yield of ATP. Anaerobic respiration occurs where oxygen is not readily available, and is much less efficient

Whilst the common respiratory pathway for both types of respiration occurs in the cytoplasm, the bulk of aerobic respiration actually occurs in the **mitochondrion**, an organelle with a double membrane. Processes within aerobic respiration occur in the matrix and the inter-membrane space between the two surrounding membranes

The Mitochondrion

The mitochondrion consists of the mitochondrial matrix where the link reaction and Krebs cycle occur. This is the interstitial fluid within the organelle. The matrix is readily equipped with all the substances required for the cell to undergo aerobic respiration (including the coenzyme NAD and the cofactor FAD, and compounds such as co-A and oxaloacetate)

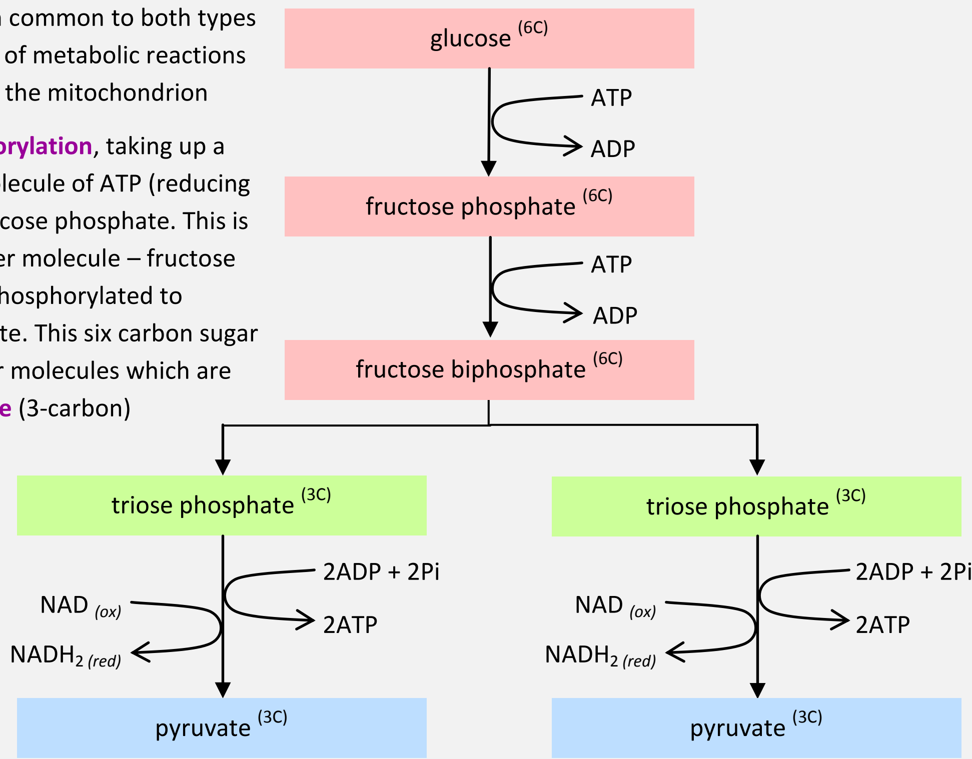
The inner membrane is lined with huge numbers of cytochromes to allow for the electron transport chain, so that chemiosmosis can occur. There are also **stalked particles** in this membrane (which are ATPase)

Glycolysis

The first stage of respiration common to both types is **glycolysis**. This first series of metabolic reactions occurs in the **cytoplasm** not the mitochondrion

Glucose undergoes **phosphorylation**, taking up a phosphate group from a molecule of ATP (reducing it to ADP) and becoming glucose phosphate. This is then rearranged into another molecule – fructose phosphate, which is again phosphorylated to become fructose biphosphate. This six carbon sugar is then split into two smaller molecules which are each called **triose phosphate** (3-carbon)

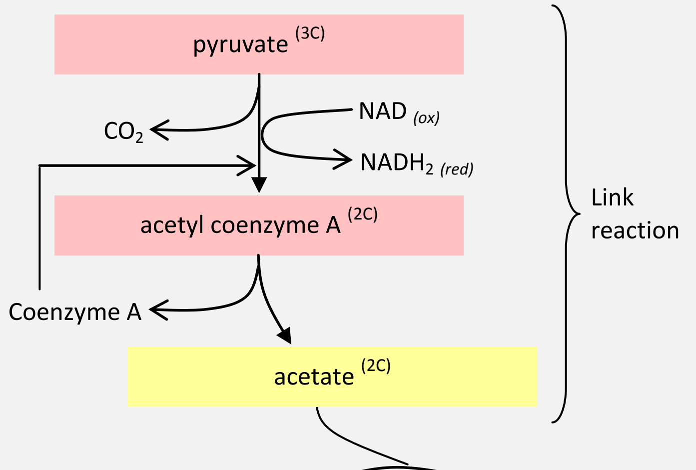
Finally, two molecules of ADP are phosphorylated for each triose phosphate to become ATP, and the sugar then has two hydrogen atoms removed using dehydrogenase enzymes to become a molecule known as **pyruvate**



The hydrogen atoms are accepted by a coenzyme called **NAD** (nicotinamide adenine dinucleotide), reducing the coenzyme to **reduced NAD** (or $NADH_2$). Overall, as two ATP were used to phosphorylate the sugar and four were eventually made, it is said that the net ATP production per glucose molecule in glycolysis is 2 ATP. Two molecules of pyruvate and two molecules of reduced NAD were also produced

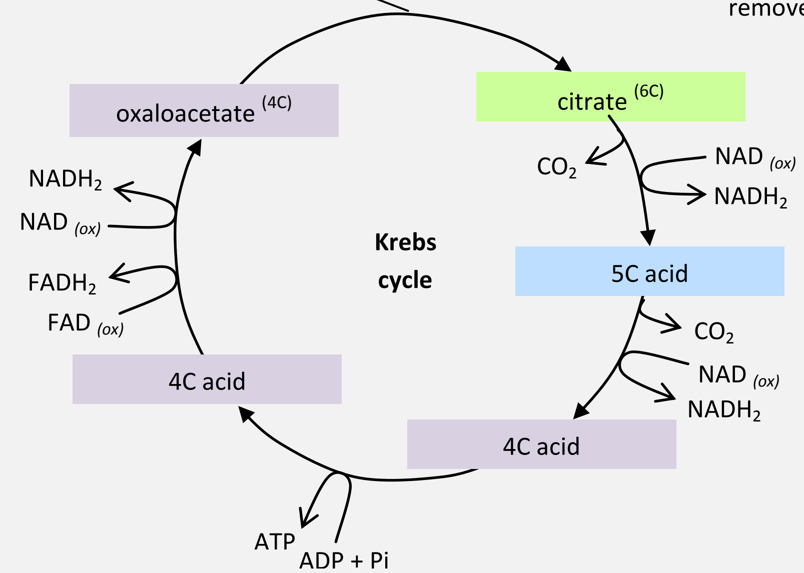
Link Reaction and Krebs Cycle

The next stage involved only in **aerobic respiration** begins with the pyruvate molecules produced from glycolysis. This part of aerobic respiration happens in the **mitochondrial matrix** and the pyruvate is transported there from the cytoplasm



In the **link reaction**, named so as it links glycolysis to Krebs, a molecule of pyruvate is first **decarboxylated** (has carbon dioxide removed) using decarboxylase enzymes and **dehydrogenated** (has hydrogen removed) using dehydrogenase enzymes. The hydrogen atoms are accepted by a molecule of NAD. The result is an **acetyl group** which binds with **coenzyme-A** to form acetyl coenzyme A. The coenzyme-A leaves the molecule (leaving it as acetate) and is recycled to be used again

The acetate is a 2-carbon molecule which then joins a molecule of **oxaloacetate** (a 4-carbon compound) to form **citrate** (a 6-carbon compound). Citrate is then decarboxylated and dehydrogenated to form a 5-carbon acid, which also has hydrogen and carbon dioxide removed, forming a 4-carbon acid. At this stage, **substrate-level phosphorylation** occurs as in glycolysis – an inorganic phosphate is removed from the compound and attached to a molecule of ADP to form ATP



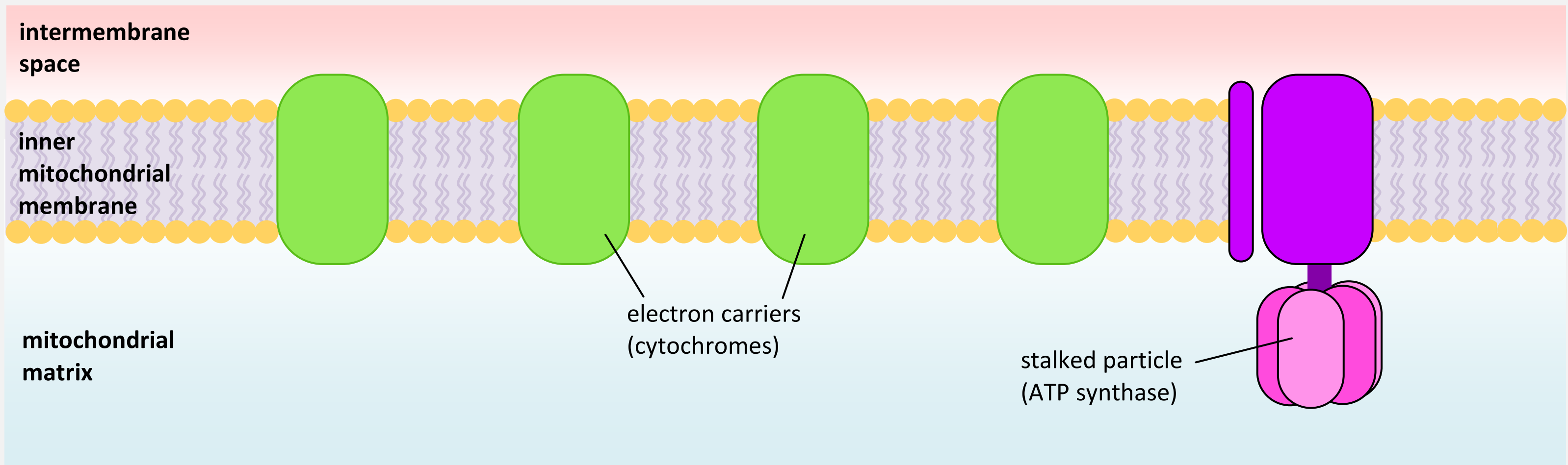
A molecule of FAD is then reduced, as is a molecule of FAD, and the removal of these four hydrogen atoms forms oxaloacetate, and so the cycle continues

There is one complete turn of the cycle for each molecule of pyruvate. The end products of Krebs cycle for each glucose include two molecules of ATP produced directly during Krebs, six lots of reduced NAD and two reduced FAD, as well as four molecules of carbon dioxide, a waste by-product. The link reaction produces a further two reduced NAD and two carbon dioxide molecules added on to this total

The molecules of reduced NAD and FAD will enter the electron transport chain and donate their accepted hydrogen atoms so that ATP can be synthesised via oxidative phosphorylation. Generally, one $NADH_2$ yields 2.5 ATP and one $FADH_2$ yields 1.5 ATP

Electron Transport Chain

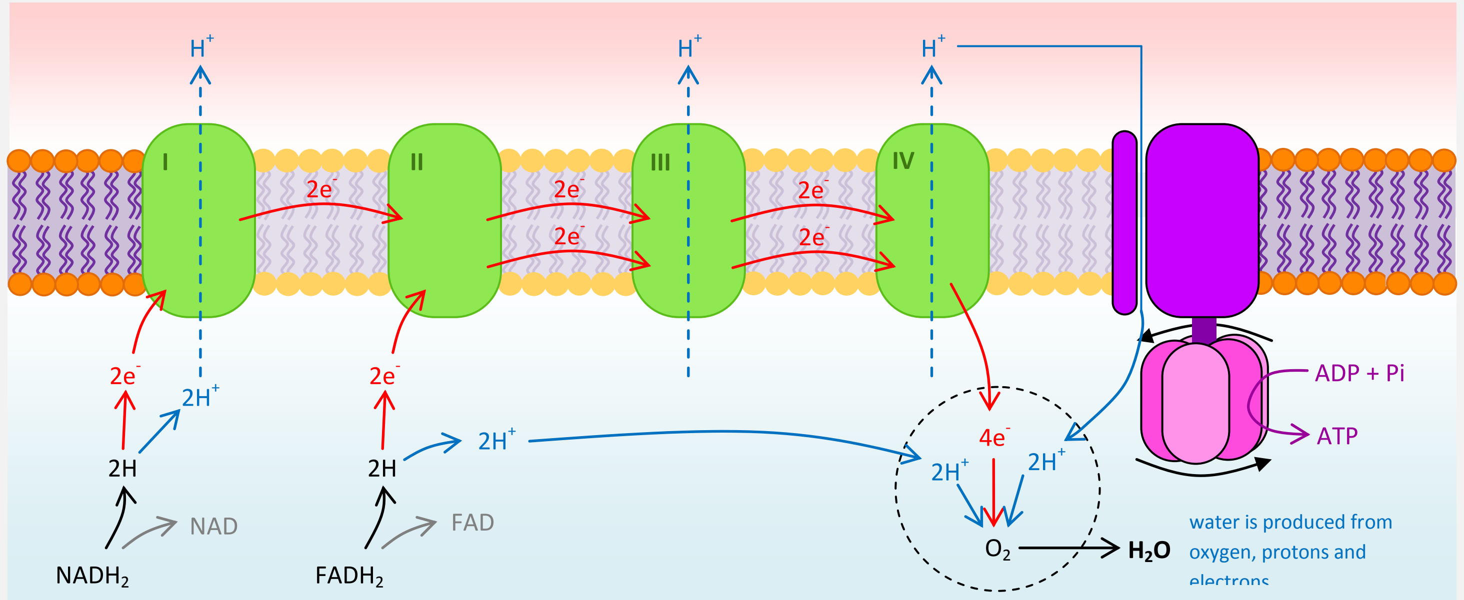
This process involves various electron carriers embedded in the inner mitochondrial membrane, called **cytochromes**. These membranes are folded into **cristae** to give a large area for many of these **electron transport systems**



Molecules of reduced NAD and reduced FAD arrive at the electron transport chain and offload the hydrogen atoms they are carrying. Each hydrogen atom can be split into a proton and an electron, and since each molecule donates two hydrogen atoms, either donates two protons and two electrons at one time. The electrons are accepted by the first cytochrome (only NAD can donate to this cytochrome) and are passed along the chain to the next carrier, cytochrome II. Further electrons will be accepted by this second cytochrome (FAD can only donate to this carrier), and again electrons are passed along to the third, and finally the fourth carrier, until leaving the chain at the end to help produce the by-product water

Chemiosmosis and Oxidative Phosphorylation

The movement of electrons from carrier-to-carrier releases energy, and at the first, third and fourth cytochromes this energy is used to pump hydrogen ions over the membrane and into the intermembrane space, between the inner and outer membranes of the mitochondrion. Eventually this builds up a high concentrations of protons in the intermembrane space, creating a concentration gradient of protons down to the matrix



As the protons develop a concentration gradient, potential energy is built up and as they cannot simply diffuse across the membrane (as charged particles) they must flow through special proton channel proteins embedded in the membrane to return to the matrix side of the membrane. This flow of electrons is called **chemiosmosis**. Chemiosmotic theory was suggested first by Peter Mitchell

The channel proteins which the protons flow back through are associated with an enzyme also embedded in the membrane called **ATP synthase** (or ATPase). As protons diffuse through the channel protein, a **proton motive force** is generated which is used to drive the rotation of the stalked particles on ATP synthase. The rotating enzyme causes one ADP molecule to join to a phosphate group to become ATP: this is ATP synthesis. This process is known as **oxidative phosphorylation**

Due to the concentration gradient established by the active flow of protons over the membrane to the intermembrane space, there is always a high concentration of protons on that side of the membrane – this ensures there is a concentration gradient, and so chemiosmosis ensues – protons are going to transport back across the membrane through channels which drive ATP synthesis

The Products of Respiration

Number of molecules made for every molecule of glucose			
Name of molecule produced	Stage of aerobic respiration		
	Glycolysis	Link reaction	Krebs cycle
ATP	2	0	2
$NADH_2$	2	2	6
$FADH_2$	0	0	2

Each $NADH_2$ yields approximately 2.5 ATP on average from the hydrogen atoms it donates to the electron transport chain, and each $FADH_2$ yields around 1.5 ATP, because FAD is simply a lower energy molecule. The table displays the number of each molecule obtained in the stages of aerobic respiration. Per glucose, in total there are 10 reduced NAD and 2 reduced FAD produced as well as 4 extra ATP from glycolysis and Krebs

Ten molecules of $NADH_2$ yields about 25 ATP. Two molecules of $FADH_2$ yields about 3 ATP. Added with those 4 ATP (2 net produced from glycolysis and 2 for the two turns of Krebs cycle), each glucose molecule should yield 32 net molecules of ATP. However, this amount is rarely achieved, for a number of reasons, including:

- some of the protons leak back across the mitochondrial membrane, so there is less of a build up to generate as much of a proton motive force, so fewer ATP are synthesised
- some ATP is used to actively transport the pyruvate molecules from glycolysis (in the cytoplasm) into the mitochondrion, and so these used up ATP molecules need to be accounted for
- similarly, the NAD and its two hydrogen atoms produced during glycolysis need to be shuttled into the mitochondrion

Anaerobic Respiration

The majority of **anaerobic respiration** is the simple glycolysis pathway. The electron transport chain needs to use oxygen as its final acceptor (to produce water), so without oxygen, no more hydrogen can be offloaded from $NADH_2$ or $FADH_2$ – so the electron transport chain stops. Pretty soon, Krebs cycle and the link reaction also stop, as no more NAD or FAD can be reduced

Mammalian anaerobic respiration is **lactate fermentation** which is a simple modified form of glycolysis. However in this process, the pyruvate molecules are the ultimate hydrogen acceptors (in order to reoxidise the reduced NAD). When pyruvate accepts the two hydrogens, it forms **lactate** (catalysed by the enzyme lactate dehydrogenase). When oxygen becomes available again after some time, the lactate is converted back to pyruvate to be respired aerobically (the oxygen required to recover is **oxygen debt**)

In yeast, **alcoholic fermentation** occurs. Glycolysis takes place as per usual, but then the pyruvate is decarboxylated to form **ethanal** (catalysed by pyruvate decarboxylase). It is then ethanal which accepts the hydrogen atoms from reduced NAD, reducing ethanal to **ethanol** (catalysed by ethanal dehydrogenase). The reoxidised NAD can then be reused to produce more ATP

As each of these processes use only glycolysis to produce ATP, only 2 molecules of ATP are produced per glucose molecule, so this is not very efficient, especially for mammals, and lactate should not be allowed to build up. Although yeast can survive anaerobic conditions, if ethanol (toxic) build up beyond a concentration of 15% yeast cells will die

Respiratory Substrates

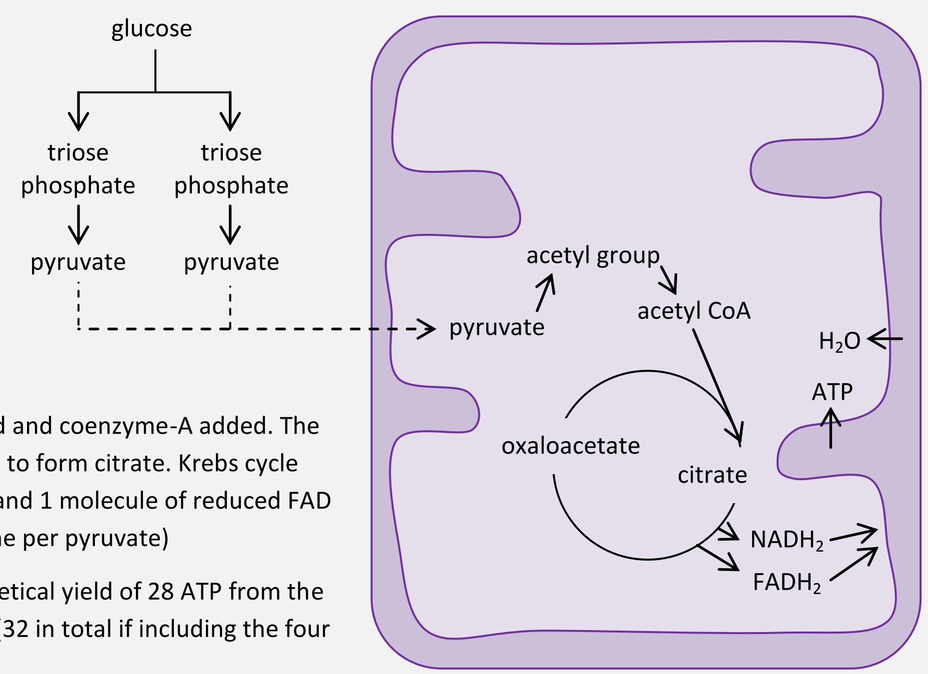
The organic compound which is respired either aerobically or anaerobically is called the **respiratory substrate**. Most usually, this is the carbohydrate glucose. However, this is not the only substrate available. As ATP is largely generated during the electron transport chain, driven by the flow of protons across the mitochondrial inner membrane, the more hydrogens available in the respiratory substrate, the more ATP will be produced during oxidative phosphorylation

Some proteins are hydrolysed to amino acids which can be converted into pyruvate or acetate to enter the link reaction and Krebs cycle to be respired. NAD accepts slightly more hydrogens from each mole of protein than it does from glucose, so amino acids yield a slightly larger number of ATP during the electron transport chain

As for lipids, triglycerides can be hydrolysed (by the enzyme lipase) into glycerol and fatty acids. Glycerol can simply be converted into glucose and respired. Fatty acids however cannot. Fatty acids can be combined with coenzyme-A to form a fatty acid-CoA complex which is actively transported into the matrix where they are broken down into acetyl groups which continue the link reaction and then enter Krebs cycle – the rest of aerobic respiration will then proceed as normal. Due to the long hydrocarbon chains in fatty acids, there are large number of hydrogen atoms present so lipids are very efficient at producing ATP – they have an energy yield which is over double that of carbohydrates such as glucose

Aerobic Respiration: A Summary

Aerobic respiration occurs only when there is oxygen present: this is because without oxygen, the electron transport system cannot continue (as nothing is there to remove the hydrogen atoms) and so Krebs cycle also stops in the absence of oxygen



Glycolysis phosphorylates glucose twice and splits fructose biphosphate into two triose phosphates which are converted into pyruvate

In the link reaction, pyruvate is decarboxylated and coenzyme-A added. The coenzyme is removed and oxaloacetate added to form citrate. Krebs cycle produces 3 molecules of reduced NAD, 1 ATP and 1 molecule of reduced FAD for every turn of the cycle (two per glucose/one per pyruvate)

The electron transport chain produces a theoretical yield of 28 ATP from the hydrogens donated by reduced NAD and FAD (32 in total if including the four produced from glycolysis)