**Higher Human Biology Outcomes**

**UNIT 1**

**Human Cells**

**Differentiation and stem cells**

**Division and differentiation in human cells**

* Cellular differentiation is the process by which an unspecialised cell becomes altered and adapted to perform a specialised function as part of a permanent tissue
* Specialised cells are organised into tissues and organs
* Cellular differentiation depends on gene expression
* Each gene codes for a single protein such as an enzyme of structural protein
* During differentiation genes are switched on as required and then switched off again
* Once a cell becomes differentiated it only expresses the genes that produce the proteins characteristic for that type of cell. (only the genes for maintenance and the special function of the cell are switched on and all the rest are switched off)
* Differentiation produces many types of specialised cells to carry out different functions

***Stem cells*** — embryonic and tissue (adult) stem cells.

* Stem cells are undifferentiated animal cells scattered throughout the tissues of the body
* Stem cells differentiate into specialised cells
* Stem cells can continue to divide
* Stem cells can differentiate into specialised cells of one or more types.
* All the genes of embryonic stem cells have the potential to be switched on, so the cell is capable of differentiating into all the types of cells in the body- Stem cells are pluripotent
* During embryological development the unspecialised cells of the early embryo differentiate into cells with specialised functions.
* Adult stem cells are found in e.g. skin and bone marrow
* Tissue (adult) stem cells can only give rise to a limited range of cell types closely related to the tissue in which they are found.
* Tissue stem cells are multipotent
* Those found in bone marrow can differentiate into red blood cells, white blood cells (phagocytes and lymphocytes) and platelets.

***Differentiation in Somatic cells***

* Somatic cells are all body cells except gametes
* Somatic cells form several different types of body tissue
* Somatic cells divide by mitosis to form more somatic cells
* These differentiate to form different body tissue types: epithelial, connective, muscle and nerve.
* The body organs are formed from a variety of these tissues.
* Epithelial cells cover the body surface and line body cavities, connective tissue includes blood, bone and cartilage cells, muscle cells form muscle tissue and nerve cells form nervous tissue.
* During cell division the nucleus of a somatic cell divides by mitosis to maintain the diploid chromosome number and ensuring that each cell receives a complete set of genetic information
* Diploid cells have 23 pairs of homologous chromosomes.
* Mutations in somatic cells are not passed to offspring.

***Germline cells***

* A germline cell is one that leads to the formation of gametes
* A germline cell is diploid and divides by mitosis to produce more germline cells
* Germline cells are able to undergo a second type of division called meiosis to form gamete cells
* Gamete cells are haploid, they contain a single set of 23 chromosomes
* Mutations in germline cells are passed to offspring.

***Research and therapeutic uses of stem cells***

* Stem cell research provides information on how cell processes such as cell growth, differentiation and gene regulation work.
* Stem cells can also be used as model cells to study how diseases develop or for drug testing.
* Stem cells can be used to treat cancer of the blood. By destroying a patient’s cancerous bone marrow cells by radiation or chemotherapy and replacing them with a bone marrow transplant of normal blood forming stem cells
* Stem cells can also be used to produce skin grafts using the patient’s own skin cells. A small sample of skin is taken and stem cells are isolated then cultured. The suspension is then sprayed over the affected area and they bring about the regeneration of the missing skin
* Stem cells are used for corneal repair. Corneal tissue can be grown by harvesting stem cells from the edge of the patient’s cornea. This tissue is then transplanted to the surface of the damaged cornea.

***Ethical issues***

* Sources of stem cells include embryonic stem cells, tissue stem cells and attempts to reprogram specialised cells to an embryonic state.
* Ethical issues surrounding the use of embryonic cells include the destruction of the human embryo when extracting the human embryonic stem cells
* Regulations on the use of embryonic stems cells include—embryo cells must not be allowed to develop beyond 14 days, around the time a blastocyst would be implanted in a uterus
* Induced pluripotent stem cells are differentiated cells that have been genetically reprogrammed using transcription factors to turn back on some of the genes which have been switched off. As a result they act as stem cells. Concern arises however as the viruses used to deliver the transcription factor have been shown in mouse models to produce cancerous cells.
* Nuclear transfer techniques involve removing the nucleus from an egg and replacing it with the nucleus from a donor cell
* Using this technique a nucleus from a human cell e.g. skin can be introduced into an enucleated animal cell e.g. an egg cell from a cow forming a cytoplasmic hybrid cell. Once it begins to divide stem cells can be extracted after 5 days and up to 14 days and used for research.
* Some people feel that it is unethical to mix materials from human cells with those of another species.

***Cancer cells***

* Cancerous cells divide excessively to produce a mass of abnormal cells (called a tumour) that fail to respond to regulatory signals
* Most cancers originate from a cell that has undergone a succession of mutations to the genes involved in the control of cell division
* A benign tumour remains as a discrete mass of abnormal cells within an otherwise healthy tissue
* A malignant tumour results if some of its cells lose the surface molecules that keep it attached to the original cell mass and they enter the circulatory system spreading through the body invading other tissues and cause secondary tumours

**DNA and its replication**

* All cells store their genetic information in the base sequence of DNA.
* The genotype is determined by the sequence of DNA bases.
* The structure of proteins is determined by the sequence of DNA bases
* DNA is the molecule of inheritance and can direct its own replication.
* The Genome is all the DNA of a species

***Structure of DNA***

* Chromosomes consist of tightly coiled DNA and are packaged with associated proteins.
* DNA is made up of two strands of nucleotides twisted into a double helix
* DNA nucleotides are composed of a deoxyribose sugar, a phosphate and one of four bases
* In DNA the base adenine (A) always pairs with thymine (T) and the base guanine (G) is complementary with cytosine (C)
* The sugar and the phosphate form the backbone of a DNA molecule
* The complementary base pairs are joined by weak hydrogen bonds
* 3’ represents carbon 3 of the sugar molecule and 5’ represents carbon 5 of the sugar molecule
* The phosphate is joined to carbon 5 of the deoxyribose and the base is joined to carbon 1
* Carbon 3 of the deoxyribose sugar is joined to the phosphate of the adjacent nucleotide
* The double helix has two antiparallel strands as their 5’ to 3’ carbons run in opposite directions.
* Prior to cell division, DNA is replicated by DNA polymerase. This process occurs at several locations on a DNA molecule.

***Replication of DNA*** by DNA polymerase and primer.

* Both polymerase and ligase enzymes join nucleotides together
* DNA polymerase is involved in DNA replication
* The enzyme DNA ligase joins nucleotides at the ends of fragments together on lagging strand
* The steps in DNA replication are:
  + The DNA double helix is untwisted and unzipped by enzymes
  + Unzipping starts at many points along the DNA molecule simultaneously
  + A short length of RNA nucleotides called a primer binds to both strands to show the DNA polymerase where to begin
  + Free DNA nucleotides join to the exposed bases forming complementary pairs
  + DNA polymerase joined adjacent nucleotides together
  + Polymerase can only extend the nucleotides from a primer in a 5’ to 3’ direction
  + New nucleotides are added to one strand continuously (the leading strand)
  + Nucleotides have to be added to the other strand in the direction going away from the unzipping
  + Primers have to beaded frequently to keep up with unzipping and short stretches of nucleotides joined together in the 5’ to 3’ direction (lagging strand)
  + DNA ligase joins together the nucleotides that fill the gap once the primers are removed

**RNA, transcription and translation**

***Gene expression****.*

* A cell’s genotype is determined by the sequence DNA bases in its genes
* A cell’s phenotype is determined by the proteins that are synthesised when the genes are expressed
* Only a fraction of genes in a cell are expressed
* Gene expression is controlled by the regulation of both transcription and translation.
* Gene expression is influenced by environmental factors acting inside (intracellular) and outside (extracellular) the cell

***RNA***

* The nucleic acid RNA is a single strand made up of RNA nucleotides
* RNA nucleotides are composed of a ribose sugar instead of deoxyribose sugar, a phosphate and one of the bases adenine (A), uracil (U), which replaces thymine, guanine (G) or cytosine (C)
* RNA has three important roles:
  + As messenger RNA (mRNA) which carries a copy of the genetic information from the nucleus to the ribosomes in the cytoplasm
  + As transfer RNA (tRNA) which brings specific amino acids to the ribosome for protein synthesis
  + The ribosomes themselves are also manufactured from ribosomal RNA (rRNA) and proteins in a part of the nucleus known as the nucleolus

***Transcription of DNA***

* mRNA is transcribed (assembled) in the nucleus using a short length of DNA ( or gene) as its template
* RNA polymerase binds to the promoter region of the DNA then moves along a short length of DNA unwinding and unzipping the double helix by breaking the weak hydrogen bonds. RNA polymerase stops when it comes to the terminator region on the strand. Energy is required from ATP.
* A primary transcript of RNA is formed as free nucleotides join to the exposed DNA bases on one DNA strand by the pairing of complimentary bases
* RNA uracil pairs with DNA adenine, RNA adenine pairs with DNA thymine and cytosine pairs with guanine
* Adjacent RNA nucleotides join phosphate to ribose sugar giving a single strand
* mRNA primary transcript peels away from the DNA which rezips
* DNA contains non coding regions called introns which are interspersed between the coding regions called exons
* The introns are cut out and removed from the primary transcript of the mRNA and the exons are spliced together to form mRNA. This process is called RNA splicing
* The mature RNA passes out of the nucleus into the cytoplasm where it becomes translated into a sequence of amino acids

***Translation of mRNA***

* Translation is the synthesis of protein as a polypeptide chain
* mRNA is made up of a series of base triplets called codons
* mRNA attaches to ribosomes on the rough ER or free in the cytoplasm
* tRNA is composed of a single strand of nucleotides which folds due to hydrogen bonds forming between its nucleotide bases this results in the formation of a triplet anticodon and an attachment site for a specific amino acid
* the tRNA anticodon and mRNA codon are complementary
* Triplet codons on mRNA and anticodons translate the genetic code into a sequence of amino acids which are brought together at the ribosome and joined with peptide bonds to form a polypeptide of protein
* tRNA exits the ribosome as the polypeptide is formed
* the mRNA has a specific codon that acts as a start codon and codons which act as stop codons
* translation requires energy from ATP

**Proteins, mutations and genetic disorders**

***One gene, many proteins***

* A variety of proteins can be expressed from the same gene as a result of alternative splicing
* Different mRNA molecules are produced from the same primary transcript depending on which RNA segments are treated as exons and introns
* Therefore one gene can code for several different proteins
* Post translational modifications (after translation is complete) may be required to enable a protein to perform its specific function
* A single polypeptide chain may need to be cut (cleaved) by enzymes to become active eg for insulin to become active the middle section must be cleaved by protease resulting in two polypeptide chains held together by sulphur bridges
* Protein structure can also be modified by the addition of a carbohydrate component or phosphate group
* For example mucus is a glycoprotein consisting of protein and added carbohydrate, regulatory proteins eg p53 requires the addition of a phosphate through phosphorylation to become activated and bring about DNA repair

***Genes and proteins in health and disease***.

* Proteins have a large variety of structures and shapes resulting in a wide range of functions.
* Proteins are made up of chains of amino acids linked by peptide bonds
* The amino acid chain is folded and held in place by hydrogen bonds to give a secondary structure
* Additional folding gives the tertiary structure which gives the protein the shape needed for it’s function
* Non protein molecules are incorporated into some tertiary structures to form a quaternary structure e.g. haemoglobin contains iron
* Proteins are held in a three dimensional shape by peptide bonds, hydrogen bonds and interactions between individual amino acids
* Hydrogen bonds form between certain amino acids in a polypeptide chain causing the chain to become coiled or folded
* Interaction between individual amino acids on different chains causes cross connections e.g. sulphur bridges to form resulting in the final three dimensional structure for its specific function
* Functions of protein include:
  + Enzymes e.g. amylase
  + Structural proteins e.g. a component of the cell membrane
  + Hormones e.g. insulin
  + Antibodies

***Mutations***

* A mutation is a random unpredictable change in the sequence or number of DNA molecules which results in changes in the genotype of a cell
* When a mutation in a genotype results in a change in phenotype the affected individual is called a mutant
* Mutations are relatively rare and occur spontaneously
* They give rise to new alleles which have not existed before and are a major source of variation in populations
* Mutations result in no protein or the proteins expressed not functioning correctly
* This results in genetic disorders
* There are two main types of mutation, chromosome mutations and gene mutations
* Chromosome mutations are changes either in the number of chromosomes, or in the structure of an individual chromosome involving more than one gene
* Single gene mutations involve the alteration of a DNA nucleotide sequence as a result of the substitution, insertion or deletion of nucleotides.

***Gene mutations***

* + Substitution one base exchanged for another
  + Insertion , a base is added can result in Tay-Sachs syndrome
  + Deletion, a base is removed can result in Cystic fibrosis
* Nucleotide insertions or deletions result in frame-shift mutations or an expansion of a nucleotide sequence repeat and affect many amino acids as the triplets which are read as the code are changed resulting in a change of the protein being coded for
* Nucleotide sequence repeat expansion results in extra copies of a particular amino acid or the gene may be silenced and fails to express any protein for example in Fragile X syndrome and Huntingdon’s disease
* A change in one nucleotide in the DNA sequence (substitution) results in one amino acid being changed this is referred to as a point mutation
* Single-nucleotide substitutions include: missense (replacing one amino acid codon with another),can result in Sickle cell disease, PKU
* nonsense (replacing an amino acid codon with a premature stop codon — no amino acid is made and the process stops) can result in Duchenne muscular dystrophy (DMD)
* splice-site mutations(creating or destroying the codons for exon-intron splicing) resulting in Beta (β) thalassemia

***chromosome mutations***

* The structure of a chromosome can be altered.
  + Deletion, loss of a segment of a chromosome can result in Cri-du-chat syndrome (deletion of part of the short arm of chromosome 5)
  + Duplication, repeat of a segment of a chromosome
  + Translocation, a section of one chromosome breaks off and becomes attached to another chromosome can result in Chronic myeloid leukaemia (CML) (reciprocal translocation of a gene from chromosome 22 fused with a gene on chromosome 9)
  + The vast majority of Down’s syndrome cases results from an extra copy of chromosome 21, however in about 5% of cases one parent has the majority of chromosome 21 translocated to chromosome 14 resulting in Familial Down’s syndrome
* A mutation to a chromosome usually involves a substantial change to its structure that a mutation is lethal

**Human genomics.**

***Sequencing DNA.***

* Human genomics is the study of the human genome
* It involves determining the sequence of the nucleotide base molecules along the DNA
* The sequence of bases can be determined for individual genes and entire genomes.
* We are able to determine entire genomes as a result of the human genome project and compare individual genomes using single nucleotide polymorphisms (SNPs).
* **Bioinformatics** is the use of computer technology to identify DNA sequences
* The enormous amount of data produced by DNA and protein sequencing can be managed and analysed using computer technology and shared over the internet
* Computer programs can be used to identify
  + gene sequences by looking for coding sequences similar to known genes,
  + start sequences – there is a good chance that each of these will be followed by a coding sequence
  + sequences lacking stop codons –a protein coding sequence is normally a very long chain of base triplets containing no stop codon except the one at its end
* Computer programs can be used to search and identify base sequences to see if it matches a specific amino acids sequence already known to be typical of a certain protein
* **Systematics** can be defined as the study of a group of living things with respect to their diversity, relatedness and classification
* Systematics compares human genome sequence data and genomes of other species to provide information on evolutionary relationships and origins
* **Personalised medicine** aims to make use of an individuals personal genome sequence
* Analysis of an individual’s genome may lead to personalised medicine through understanding the genetic component ( an altered genetic sequence) of risk of disease.
* The information gained from DNA studies can provide information on the structure of the genes and proteins involved in disease.
* Once mutant variants have been located in the genome it is important to distinguish between neutral (no harmful effect) and harmful mutations
* Once a mutation in the DNA sequence has been identified a link between the mutation and a disease has to be established.
* The nature of disease is highly complex depending on both genetic and environmental factors for expression
* **Pharmacogenetics** is the study of the effects of pharmaceutical drugs on the genetically diverse members of the human population
* Once DNA sequencing has identified the genes involved in a specific disease and also established the structure of the protein expressed the Pharmacogenetisists can try to synthesise a specific drug. This is known as rational drug design.
* The drug produced will bind to the proteins involved or prevent their synthesis by binding to a specific region of DNA preventing transcription of abnormal mRNA or by binding to the abnormal mRNA preventing translation, for example interfering RNA (RNAi)

***Amplification and detection of DNA sequences****.*

* Polymerase chain reaction (PCR) is a technique that replicates short lengths of DNA quickly
* Amplification of a piece of DNA using PCR is an in vitro (outside the body) process.
* The amplification of DNA involves the use of complementary primers for specific target sequences of the DNA
* In PCR, primers are complementary to specific target sequences at the 3’ end of the two ends of the region to be amplified.
* DNA is heated to separate the DNA strands
* It is then cooled to allow the primers to bind to the target sequences of DNA
* Heat tolerant DNA polymerase then adds nucleotides to the primers at the 3’ end of the original DNA strands.
* Repeated cycles of heating and cooling amplify the region of DNA.
* In an hour one short length of DNA can become a million
* Arrays of DNA probes are used to detect the presence of specific sequences in samples of DNA.
* An array is an orderly arrangement of many items therefore an array of DNA probes is the orderly arrangement of thousands of different DNA probes
* The probes are short single stranded fragments of DNA that are complementary to a specific sequence.
* A fluorescent label is attached to the probe to allow detection

***Applications of DNA profiling***

* DNA profiling enables the identification of individuals by comparing the regions of the genome with highly variable numbers of repetitive sequences of DNA.
* By screening a cell sample from a patient for the presence or absence of a particular DNA sequence, a diagnosis of disease status or risk of disease onset can be made.

**Metabolic Pathways**

***Cell metabolism***

* Cell metabolism is the collective term for the biochemical reactions that occur in a living cell
* Many of these biochemical reactions are steps in a complex network of connected and integrated pathways that are catalysed by enzymes
* There are two types of metabolic pathways
  + Anabolic – requires energy—brings about the biosynthesis of complex molecules from simpler building blocks
  + Catabolic – releases energy and is involved in the breakdown of molecules
  + These metabolic pathways can have reversible, irreversible steps which keep the process under strict control
  + An example of an irreversible step is the diffusion of glucose into a cell from a high to low concentration
  + Metabolic pathways can also have alternative routes that allow steps in the pathway to be bypassed

***Control of metabolic pathways***

* Metabolic pathways are controlled by the presence or absence of particular enzymes in the metabolic pathway
* If the appropriate enzyme is present the pathway continues , if the enzyme is absent the pathway stops
* Enzymes action can be regulated at the level of gene expression and at the level of enzyme action
* Regulation can be controlled by intra- and extracellular signal molecules
* Genes for some enzymes are continuously expressed. These enzymes are always present in the cell and their control involves regulation of their rate of reaction.
* Most metabolic reactions are reversible and the presence of a substrate or the removal of a product will drive a sequence of reactions in a particular direction. E.g. lactose metabolism in *E. coli*
* Lactose is digested to glucose in the presence of the enzyme beta galactosidase
* The gene to make the enzyme is called the structural gene
* The structural gene only switches on in the presence of lactose
* This saves the energy that would be wasted in order to produce the enzyme when it is not needed
* The structural gene is controlled by an operator gene next to it
* When lactose is absent a repressor molecule attaches to the operator gene
* The lactose prevents the operator gene from switching on the structural gene
* The repressor molecule is produced by a regulator gene
* When lactose is present, some of it combines with the repressor molecule
* This prevents it from attaching to the operator
* Without the repressor molecule the operator gene is free to switch on the structural gene
* This means that the enzyme is produced and continues to be produced until it has digested all the lactose
* When the lactose is gone, the repressor molecule is released and returns to the operator gene which then prevents the structural gene from producing the enzyme until the next time that lactose is present
* The group of genes operating together in this way is called an operon
* The molecules which causes the switching on and off( lactose in this case) is called the inducer

***Induced fit***

* Part of a substrate molecule fits into the active site of the enzyme
* Charged groups on the substrate are complementary to charged groups in the active site
* Enzymes are specific to their substrate because the two molecules must be compatible in every respect for the reaction to take place
* Once the correct substrate binds the shape of the enzyme changes to its working conformation
* This is known as induced fit

***Activation energy***

* The energy required to break chemical bonds in the reacting chemicals is called the activation energy
* The bonds break when the molecules of a reactant have absorbed enough energy to make them unstable
* This is called the transition state and the reaction can now take place
* Lowering the activation energy of the transition state causes the release of products which have a low affinity for the active site
* Enzymes lower the activation energy required for a reaction to take place

***The effects of substrate and end product concentration***

* The rate of a reaction is affected by substrate concentration. When substrate concentration is low all the active sites on the enzymes will not be occupied. The rate of reaction is slow
* Increasing substrate concentration will cause the rate of reaction to increase as more active sites will be occupied.
* When all the active sites are occupied increasing substrate concentration does not give rise to an increase in reaction rate.
* A metabolic pathway usually involves a group of enzymes
* A group may take the form of a multi enzyme complex
* Enzymes such as DNA polymerase and RNA polymerase form part of multi enzyme complexes
* Metabolic pathways are controlled by switching on or off the enzyme at the start of the pathway
* If the first enzyme is switched off the rest of the pathway stops due to the lack of intermediates
* The first enzyme can be inhibited by high levels of the final product of the whole pathway
* High level mean that the end product is not being used and it is wasteful to make more
* This is known as end product inhibition
* This is a form of negative feedback because high concentrations of the end product causes the pathway which produces it to be switched off

***Competitive inhibition***

* A competitive enzyme inhibitor has a similar shape to the substrate and so competes for the active site which prevents the substrate molecule entering resulting in a non functioning enzyme
* As the proportion of competitive inhibitor to substrate increases the rate of reaction decreases
* Non competitive enzyme inhibitors bind to the enzyme permanently and change the shape of the active site which prevents the substrate molecule entering resulting in a non functional enzyme
* Non competitive inhibitors reduces the rate of reaction whatever the substrate concentration

***Cellular respiration***

***The role of ATP***

* Respiration occurs in every living cell
* Some cells are more active, eg muscle cells, and so need more ATP
* ATP is a short term transferable store of chemical energy which is required for most cell processes eg active transport of glycolysis or unzipping DNA
* ATP is synthesised, or regenerated from ADP and inorganic phosphate or Pi through a process called phosphorylation. ( the addition of a phosphate group to a molecule)
* There is a constant supply of ATP in a cell because it is synthesised as fast as it is used
* The metabolic pathways of cellular respiration are central to metabolism. They yield energy and are connected to many other pathways.

***Production of ATP***

***Glycolysis***

* The breakdown of glucose to pyruvate in the cytoplasm in glycolysis
* Glycolysis is a series of enzyme controlled steps
* Those in the first half of the chain make up the energy investment phase where 2ATP are used up per glucose molecule
* Those in the second half of the chain make up an energy payoff phase where 4ATP are produced per glucose molecule
* Phosphorylation of intermediates during the first phase occurs twice
* The phosphorylation of intermediates in glycolysis in an energy investment phase and the direct generation of ATP in an energy pay-off stage.
* The first phosphorylation leads to a product that can continue to a number of pathways e.g. fermentation in the absence of oxygen
* The second phosphorylation, catalysed by phosphofructokinase, is an irreversible reaction leading only to the glycolytic pathway.
* H+ ions are also released during the energy payoff phase by a dehydrogenase enzyme
* The coenzymes NAD or FAD pick up the H+ ions to form NADH or FADH2 in glycolysis and citric acid pathways.
* NADH and FADH2 release the high-energy electrons to the electron transport chain on the mitochondrial membrane and resulting in the synthesis of ATP.

***Citric acid cycle***

* Pyruvate progresses to the citric acid cycle if oxygen is available.
* Pyruvate is broken down to an acetyl group that combines with coenzyme A to be transferred to the citric acid cycle as acetyl coenzyme A.
* Acetyl coenzyme A combines with oxaloacetate to form citrate followed by the enzyme mediated steps of the cycle.
* This cycle results in the generation of ATP, the release of carbon dioxide and the regeneration of oxaloacetate in the matrix of the mitochondria.

***Electron transport chain***

* The electron transport chain is a collection of proteins attached to a membrane.
* NADH and FADH2 release the high-energy electrons to the electron transport chain where they pass along the chain, releasing energy.
* The energy is used to pump H ions across the inner mitochondrial membrane.
* The return flow of H ions drives ATP synthase and produces the bulk of the ATP generated by cellular respiration.

***ATP synthesis***

* High energy electrons are used to pump hydrogen ions across a membrane and flow of these ions back through the membrane synthesises ATP using the membrane protein ATP synthase.
* The return flow of these ions rotates part of the membrane protein ATP synthase, catalysing the synthesis of ATP
* The final electron acceptor is oxygen, which combines with hydrogen ions and electrons to form water.

***Substrates for respiration***

* Starch and glycogen are broken down to glucose for use as a respiratory substrate.
* Other sugar molecules such as maltose and sucrose can be converted to glucose or glycolysis intermediates for use as respiratory substrates.
* Proteins can be broken down to amino acids and converted to intermediates of glycolysis and the citric acid cycle for use as respiratory substrates.
* Fats can be broken down into fatty acids and glycerol. Glycerol is converted to a glycolytic intermediate and fatty acids metabolised into fragments which enter the citric acid cycle

***Regulation of cellular respiration***

* The cell conserves its resources by only producing ATP when required.
* ATP supply increases with increasing rates of glycolysis and the citric acid cycle, and decreases when these pathways slow down.
* If the cell produces more ATP than it needs, the ATP inhibits the action of phosphofructokinase slowing the rate of glycolysis.
* High concentrations of citrate also inhibit phosphofructokinase, however if the citrate concentration drops the enzyme is then no longer inhibited and the rate of glycolysis increases, increasing the supply of acetyl groups to the citric acid cycle.
* This process of feedback inhibition regulates and synchronises the rates of the glycolytic and citrate acid cycle pathways

***Energy systems in muscle cells.***

* During strenuous muscle activity the cell rapidly breaks down its reserves of ATP to ADP and Pi and releases energy.
* Muscle cells can only store sufficient ATP for a few contractions
* Muscle cells have an additional source of energy in creatine phosphate that can be used to replenish ATP pools during rigorous bouts of exercise.
* Creatine phosphate in muscle cells breaks down releasing energy and phosphate which are used to convert ADP to ATP by phosphorylation
* This system can only support strenuous muscle activity for around 10 seconds, then the creatine phosphate supply runs out.
* When muscle energy demand is low, ATP from cellular respiration is used to restore the levels creatine phosphate.
* Creatine phosphate acts as a high energy reserve available to muscle cells during the next period of strenuous exercise

***Lactic acid metabolism.***

* During vigorous exercise, the muscle cells do not get sufficient oxygen to support the electron transport chain.
* Under these conditions the cells respire anaerobically
* Pyruvate is converted to lactic acid
* This conversion involves the transfer of hydrogen from the NADH produced during glycolysis to pyruvic acid to produce lactic acid.
* This regenerates the NAD needed to maintain ATP production through glycolysis.
* Lactic acid accumulates in muscle causing fatigue.
* The oxygen debt is repaid when exercise is complete allowing respiration to provide the energy to convert lactic acid back to pyruvic acid and glucose in the liver.

***Types of skeletal muscle fibres***

* All physical activity requires parts of the body to move
* These actions are brought about by the action of skeletal muscles
* These fall into two categories depending on their twitch duration
* Slow twitch (Type 1) muscle fibres contract more slowly, but can sustain contractions for longer and so are good for endurance activities.
* These muscle fibres are good for endurance activities like long distance running, cycling or cross-country skiing.
* Slow twitch muscle fibres rely on aerobic respiration to generate ATP and have many mitochondria, a large blood supply and a high concentration of the oxygen storing protein myoglobin.
* Myoglobin is able to extract oxygen from the blood for use by muscle cells especially those in slow twitch muscles
* The major storage fuel of slow twitch muscles fibres is fats.
* Fast twitch (Type 2) muscle fibres contract more quickly, over short periods, so are good for bursts of activity.
* These muscle fibres are good for activities like sprinting or weightlifting.
* Fast twitch muscle fibres can generate ATP through glycolysis only and have few mitochondria and a lower blood supply than slow twitch muscle fibres.
* The major storage fuels of fast twitch muscles fibres are glycogen and creatine phosphate.
* Most human muscle tissue contains a mixture of both slow and fast twitch muscle fibres.
* Athletes show distinct patterns of muscle fibres that reflect their sporting activities.