PROTEINS

BigPicture

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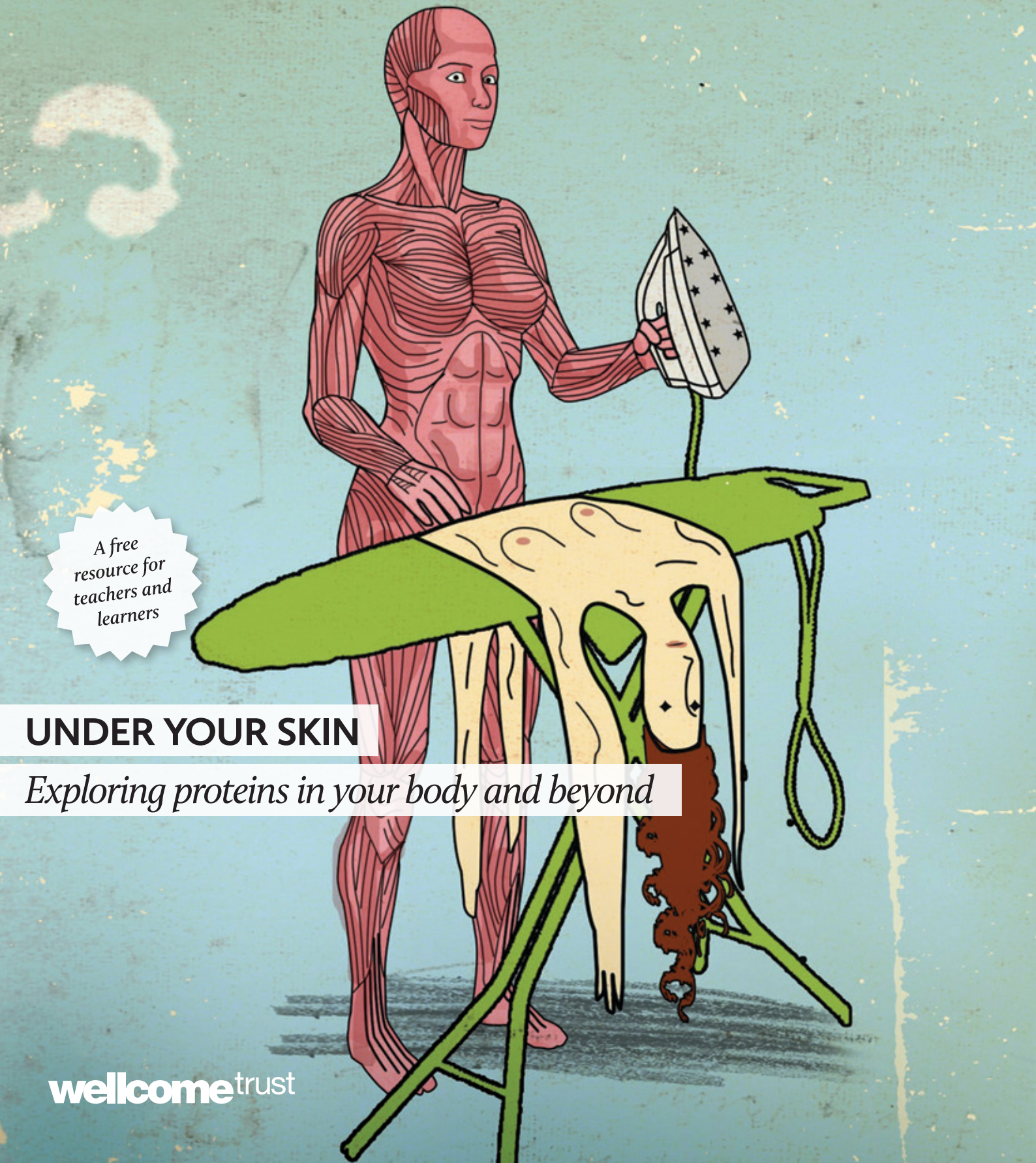
BRINGING CUTTING-EDGE SCIENCE INTO THE CLASSROOM



A free resource for teachers and learners

UNDER YOUR SKIN

Exploring proteins in your body and beyond

wellcome trust

BigPicture

Proteins are polymers of amino acids, and they do all sorts of incredible things. They give structure to living things, carry messages and molecules around our bodies, support the immune system and catalyse chemical reactions, and they are used widely in industry and medicine too. In this issue, we explore proteins by their different functions and have picked a focus protein for each. Find more resources at **www.wellcome.ac.uk/bigpicture/proteins**.

INSIDE

▸ ONLINE

Go to **www.wellcome.ac.uk/bigpicture/proteins** *for more teaching resources, including extra articles, useful web links, lesson ideas, curriculum links and more. You can also download the PDF of this magazine and subscribe to the* Big Picture *series.*

PROBING PROTEINS

A numerical look at all things protein

LEVELS OF PROTEIN STRUCTURE

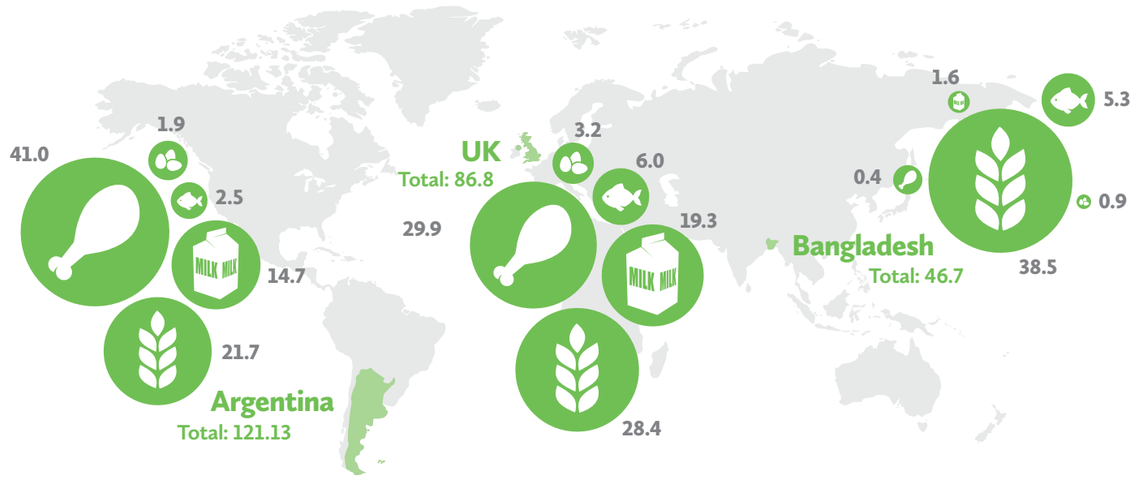
Primary: The sequence of amino acids that makes up a protein or polypeptide chain, linked by peptide bonds.

Secondary: The shape that the chain of amino acids takes, held together by hydrogen bonds.

Tertiary: The unique 3D shape that some proteins take, held together by interactions between amino acid side chains.

Quaternary: How different polypeptide chains are arranged if a protein has more than one subunit.

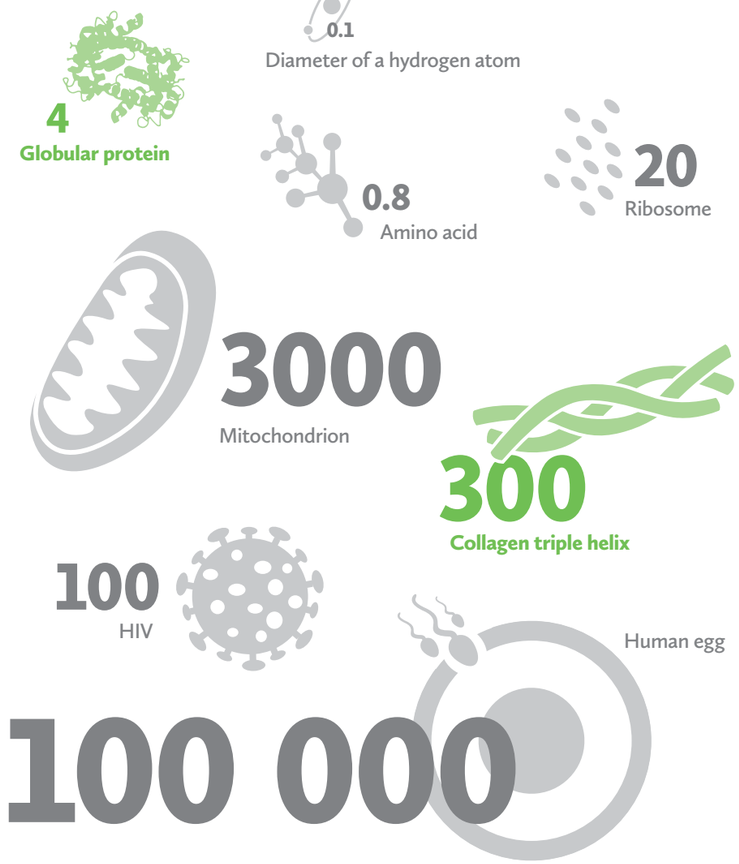
DIETARY SOURCES OF PROTEIN BY COUNTRY



All figures are in grams per capita per day, 2009.

Source: faostat3.fao.org/home/index.html. Sources are meat, eggs, fish and seafood, milk, and cereals. Other country data available.

SIZE OF PROTEINS RELATIVE TO OTHER SUBSTANCES (PROTEINS IN GREEN)



All measurements in nanometres (nm).

Source: en.wikibooks.org/wiki/Cell_Biology/Introduction/Cell_size, www.ncbi.nlm.nih.gov/pmc/articles/PMC2846778/.

HOW MANY AMINO ACIDS...?

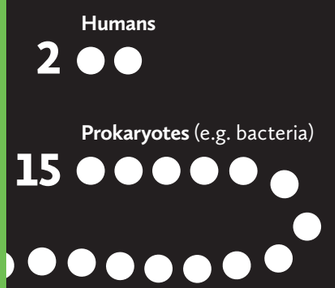
20 in human proteins

at least 700 are found in nature

10 are essential for humans

Source: www.mhhe.com/physsci/chemistry/carey5e/Ch27/ch27-1-1.html, web.expasy.org/cgi-bin/protparam/protparam1?Q8WZ42@1-34350@

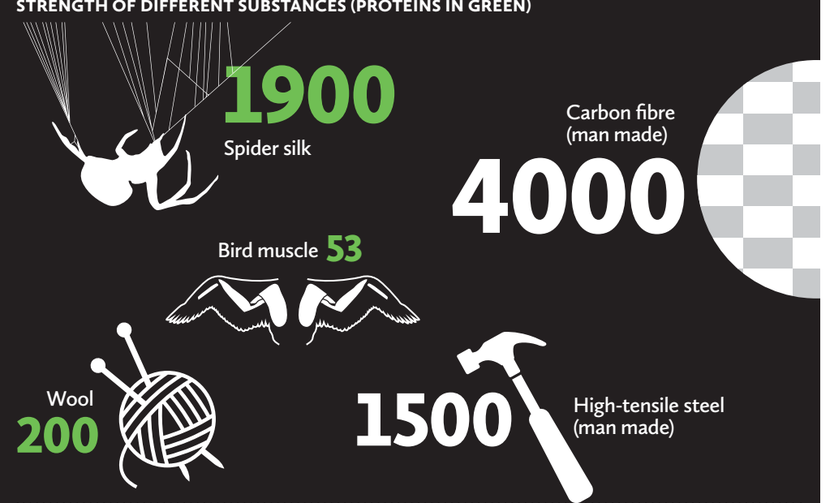
SPEED OF PROTEIN SYNTHESIS



Amino acids per second

Source: biowiki.ucdavis.edu/Genetics/Unit_III%3A_The_Pathway_of_Gene_Expression/Chapter_14:_Translation%3A_Protein_synthesis

STRENGTH OF DIFFERENT SUBSTANCES (PROTEINS IN GREEN)



Tensile strength (the force required to pull apart a substance), measured in megapascals (MPa).

Source: www.plosone.org/article/info:doi/10.1371/journal.pone.0011234

FINDING DATA

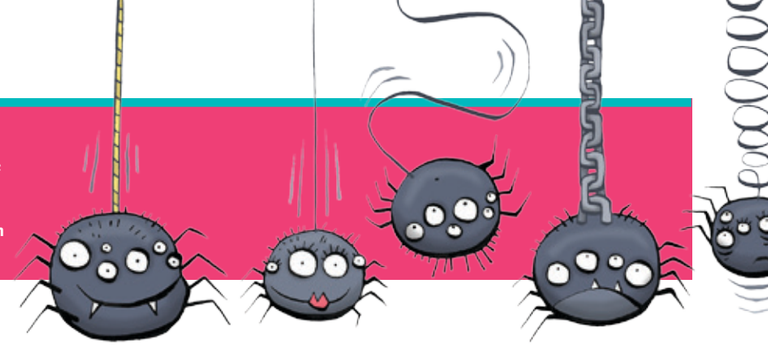
Putting this diagram together, we found that different sources gave different numbers for the same thing. Why don't they match?

Well, data can be interpreted in different ways, and estimates can be made using different methods and/or baseline data. Definitions matter, too – different sources might define 'size' or 'strength' differently.

Which should you choose? The source itself is important – is it reliable? Are the figures recent? How might an organisation's 'agenda' affect how it calculates and presents data?

STRUCTURE AND MOVEMENT

Proteins give our cells, tissues and organs structure. They help organisms, cells and their contents move.



FAST FACT

Spider silk is a strong, naturally occurring protein. There are seven types, including dragline (to attach the spider to the web) and swathing (for wrapping prey).
Source: **www.chm.bris.ac.uk/motm/spider/page2.htm**

FOCUS PROTEIN: COLLAGEN

Keeping animals in shape

Collagen comes in different varieties, but they all have the same basic structure: a sequence of three amino acids repeated hundreds of times. The sequence is Gly-Pro-X, where Gly is glycine, Pro is often proline and X is usually a modified form of proline called hydroxyproline. This amino acid sequence allows the polypeptide chain to fold into a helix (this is different from the alpha helix seen in the secondary structure of some proteins). Three collagen helices then wind round one another to form a strong, stable collagen triple helix. These helices covalently bond with each other to create fibrils, which can, in turn, be bundled into collagen fibres.

The collagen triple helix is the most common protein structure in the body. It is found in bones and teeth, tendons, ligaments and cartilage, the walls of arteries, and one of the thin layers of the cornea that protects our eyes. Altogether, around one-third of all the protein in vertebrates is collagen.

Collagen fibrils combine with other materials in the extracellular matrix, which fills the space between cells in different ways in different tissues. In bone, for example, calcium phosphate crystals form in the gaps between collagen fibres to harden it.

Partially degraded collagen from the bones and skin of animals makes gelatine, which is the substance that gives marshmallows and sweets their squishy texture.

DISCUSS

MEATY ISSUES

Discussing protein in the diet

Meat, fish, eggs, milk and cheese contain proteins with broadly the same amino acid composition as those found in our bodies. Digestion breaks these proteins down into amino acids, which are then available for reuse in roughly the proportions we need to build new proteins.

If particular amino acids are in short supply in our diet, we can make some of them from other molecules we eat. However, humans cannot make ten so-called 'essential' amino acids, so they come only from our diet. Essential amino acids include phenylalanine and tryptophan.

Vegans do not eat anything derived from animals, which means they have to get essential amino acids from other food sources. Some plant foods – including soya, quinoa and hemp – contain all the essential amino acids.

Meat is an important source of protein for many people around the world (see page 3). The global appetite for it is growing, which is putting more pressure on food production: feeding crops to animals is much less efficient than eating crops ourselves. For example, the least energy-efficient plant food uses around one-tenth as many fossil fuels as the most energy-efficient factory farming of meat.

The search is on for supplements or substitutes for meat that could help humans to avoid eating animals, ease pressure on cropland or simply offer healthier alternatives – especially to red meat, which includes saturated fat as well as protein. You can already buy meat substitutes made from a protein-rich fungus. In 2013, the first burger grown from cow stem cells was cooked and eaten. Protein powder made from farmed insects could also be a protein source of the future.

Questions

- Can you list three pros and three cons of using land to raise livestock?
- Are lab-grown burgers a promising innovation or an expensive diversion from feeding the world?
- Billions of people already eat insects regularly. Would you? Why?

For more on this topic, see the video at www.wellcome.ac.uk/bigpicture/proteins.

IMPORTANT CONNECTIONS

Collagen mutations cause disorders

Structural proteins such as collagen are made in large amounts, and any variation in their make-up is very noticeable. There are more than 30 different genes for collagen in humans, and genetic mutations can weaken the structures supported by collagen. Some mutations are fatal; others can cause problems such as slow growth and bones that break easily. Brittle bone disease, or 'osteogenesis imperfecta', arises from mutations in one type of collagen (see 'Real Voices' on pages 14–15 for more on this).

Alterations to some other forms of collagen affect connective tissue. People with Ehlers–Danlos syndrome, which is also caused by a range of different mutations, may have very stretchy skin that bruises easily and heals badly. Ehlers–Danlos syndrome can also cause weakness in heart valves, weakness in the walls of the bladder or uterus, and floppy joints.

Some of these problems arise directly from changes in collagen protein sequences. Others are caused by changes in the enzymes that alter some amino acids after the basic protein is made, a process called post-translational modification.

Those enzymes – that convert proline to hydroxyproline or lysine to hydroxylysine – also depend on vitamin C. Many of the symptoms of scurvy (vitamin C deficiency) are seen in connective tissue. Leaky capillaries cause bleeding under the skin, teeth come loose, and wounds no longer heal.

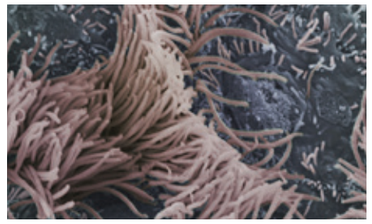
ON THE MOVE

Proteins keep cells together

Smaller structures inside cells are often made of microtubules (tube-shaped polymers of the protein tubulin). Microtubules are very versatile and have evolved to work in a range of different ways. For example, microtubules form the cytoskeleton, an internal scaffold in cells. Microtubule structures are dynamic and are constantly being built, pulled apart and rebuilt.

Cilia, thin rods that protrude from the surface of cells, are bundles of microtubules. The most basic cilia move in the ebb and flow of fluid outside the cell, sensing changes in the environment. Motile cilia can move fluid themselves instead of just being moved by it. Millions of cilia move to sweep mucus up out of the lungs into the throat, removing inhaled dust and dead cells.

Flagella, which are larger, are also tightly arranged bundles of microtubules. They help cells move and can also be involved in sensing the environment outside the cell. Eukaryotes (cells with nuclei) from any species have microtubule, cilia and flagella proteins with very similar sequences and secondary structures. As such, these proteins are 'highly conserved'. In prokaryotic cells such as bacteria, which do not have a nuclear membrane, the flagellum is made from a different protein called flagellin.



Wellcome Images

Cilia of the bronchus of the respiratory tract.

Motile cilia and flagella are powered by tiny cellular machines, which are also made from proteins. Molecular motors like this move muscles, power cilia, shift cargo along networks of microtubules inside the cell and organise chromosomes for cell division.

WHAT'S YOUR TYPE?

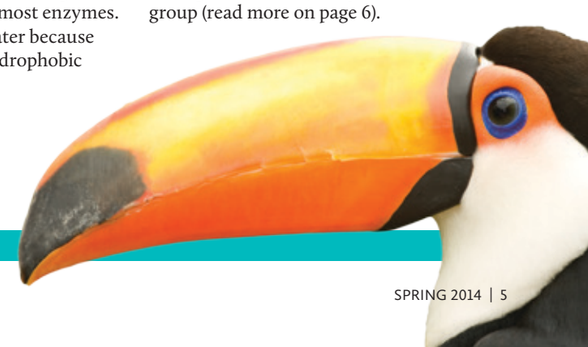
Proteins can be separated into broad groups

Fibrous proteins form long fibres and often have repeated sequences of amino acids. They are insoluble in water. Structural proteins, including collagen and keratin, are usually fibrous. They are found in the tough parts of organisms, such as bones, beaks, claws, skin, hair and feathers. Structural proteins knit together in stable arrays, with lots of cross-links to hold them together.

Globular proteins include haemoglobin, antibodies in mammals and most enzymes. They tend to be soluble in water because their 3D structure has the hydrophobic (water-hating) parts facing the centre and the hydrophilic (water-loving) parts facing the outside.

Some proteins exist within cell membranes. Read more about these on pages 7 and 10–11.

Conjugated proteins are those that include non-protein parts, such as haemoglobin. In the human form, this protein has four polypeptide chains, each arranged around a (non-protein) haem group (read more on page 6).



Shutterstock/Elnavegante

▶ **MORE ONLINE: www.wellcome.ac.uk/bigpicture/proteins**

TRANSPORT

Proteins carry substances around our bodies and act as gatekeepers to control what goes in and what comes out of cells.

FOCUS PROTEIN: HAEMOGLOBIN

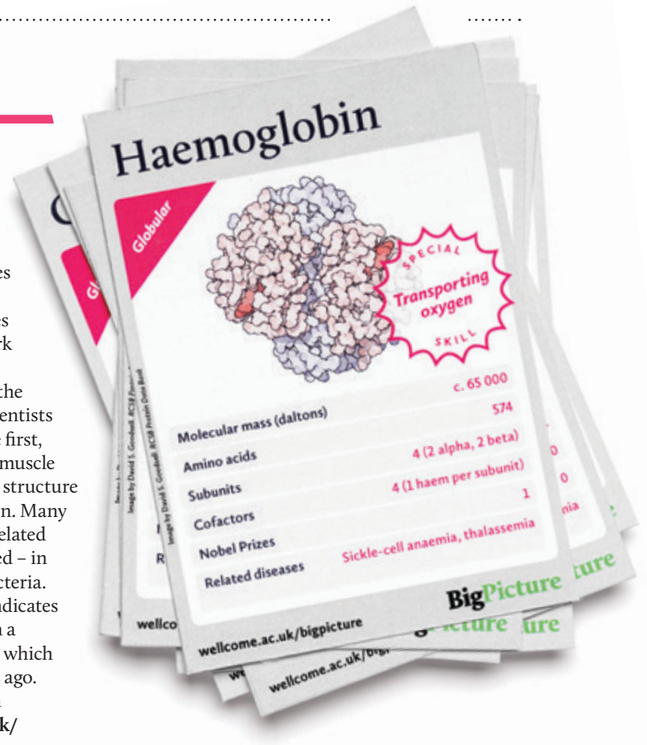
Carries oxygen around the body

Oxygen moves out of your lungs dissolved in your blood. Haemoglobin, a globular protein, contains special oxygen carriers. Each protein contains four haem groups, an iron atom cradled in a ring of four nitrogen atoms. This allows blood to carry 70 times as much oxygen as blood plasma alone.

Like many globular proteins, the globin chain has stretches of alpha helix, in which the protein chain coils around itself under the influence of electrostatic bonds, hydrogen bonds and van der Waals forces between amino acid atoms. The alpha helix, a very common secondary structure, is more tightly wound than the triple helix of collagen.

The way that the four subunits of haemoglobin interact, its quaternary structure, holds the key to its function. Four subunits each contain one oxygen-binding site. When the first iron atom takes up an oxygen molecule in the blood capillaries surrounding the lungs, that subunit changes shape. The other three then shift and 'grab hold' of any passing oxygen. In the tissues that need the oxygen, the process is reversed. Iron gives the protein and blood its dark red colour.

Horse haemoglobin was the second protein for which scientists solved the 3D structure. The first, myoglobin, binds oxygen in muscle tissue and has a very similar structure but just one amino acid chain. Many forms of haemoglobin and related proteins have been sequenced – in animals, plants and even bacteria. Comparing the sequences indicates that they all descended from a single ancestral globin gene, which first evolved billions of years ago. For more, see our animation online (**www.wellcome.ac.uk/bigpicture/proteins**).



DISCUSS

BUILDING BLOOD

Is synthetic blood a reality?

Blood transfusions save lives, but sometimes there isn't enough in the blood bank or a patient won't accept the donation (e.g. because their religious beliefs forbid it). Helping patients survive with substitutes is tricky. Whole blood does a lot more than transfer oxygen: it contains platelets, which are important in clotting; white cells, which are part of the immune system; and clotting factors in the plasma.

Researchers are trying to create oxygen carriers for blood. Current efforts involve removing haemoglobin from red cells and modifying it to keep it stable. Hemopure, developed in the USA, is a preparation of cow haemoglobin treated to make polymers of the globin subunits. These float freely in the blood and work more or less like normal haemoglobin until they are broken down, although they may increase blood pressure and raise the risk of a heart attack.

Other approaches include using haemoglobin from outdated human blood encapsulated in an artificial coating and making new blood from stem cells. No artificial haemoglobin-based oxygen carriers are in regular use, but they have been given to a handful of patients who would not normally accept blood transfusions. Jehovah's Witnesses do not accept blood transfusions, and several owe their lives to these substitutes.

Questions:

- Should doctors give patients blood against their will and without consent if they need it?
- Should doctors transfuse children if necessary, even if their parents forbid it?
- Why might some sportspeople want to use blood substitutes? Should this be allowed?

Shutterstock/Sebastian Kaulitzki

FAST FACT

Mint-flavoured things taste cold because the menthol in mint causes the activation of an ion channel protein that also responds to low temperatures.
Source: **mentalfloss.com**

CHANNELLING FAILURE

A protein problem causes cystic fibrosis

Cystic fibrosis is one of the most common conditions caused by a defective transport protein. Around 9000 people in the UK have this life-shortening condition, which has no cure. People who are affected often have repeated chest infections and problems with their digestive system.

The protein involved – the cystic fibrosis transmembrane conductance regulator, or CFTR – was named after the condition. It regulates the movement of chloride ions. A faulty version of the protein causes a change in the composition of sweat and of mucus secretions in the throat, lungs and intestines.

The CFTR protein is large (1480 amino acids) and almost 2000 different genetic mutations are known. The most common, which accounts for two-thirds of all cases of cystic fibrosis, is a deletion of three DNA bases in the CFTR protein. This removes a single amino acid, a phenylalanine, which is the 508th amino acid in the sequence. The altered protein does not fold properly and so is broken down by the cell. Other mutations produce proteins that are too short or that are present in the cell membrane but don't work as they should.

SOLVING STRUCTURES

Why do scientists study proteins' shapes?

To understand proteins fully we need to see what they look like, but even with a microscope they are too small to see. The key to 'seeing' the complex shapes of proteins was the discovery that pure proteins can be crystallised. This confirmed that they had a defined structure and meant that, in theory, their structures could be solved by X-ray crystallography. When you shine a beam of X-rays through a crystal, the regular array of protein molecules splits and diverts the beam in many directions, giving a pattern of spots that is recorded on a detector.

For simple crystals, such as diamond (which is not a protein), the maths needed to calculate the arrangement of atoms that makes a particular X-ray pattern is relatively straightforward. Proteins, with their thousands or even tens of thousands of atoms, presented a harder problem that took many years to solve. Today, big structures can often be solved using more intense X-ray sources and improved computational methods; however, not all proteins crystallise readily. Transmembrane proteins, in particular, are unstable when purified.

Protein structures are also probed with nuclear magnetic resonance, which is good for studying proteins in solution. Large protein complexes and ribosomes can be seen using electron microscopy.

One day, we may be able to predict how a protein folds from its amino acid sequence, but this is still a tough problem to solve because the number of possible shapes is astronomically large. Computer programmes have been developed to do some of the work, and scientists have tried to help them along by incorporating them into a computer game that anyone can play (**fold.it/portal/**) – try it!

CELLULAR SIGNALS

Membrane receptors are important proteins

Our cells have an outside and an inside, and more compartments within. These spaces are divided by membranes studded with proteins that control the traffic across them.

Membrane-bound proteins are numerous and hard to study. Many straddle the membrane, sticking out on both sides. The membrane itself is made of phospholipid, so membrane proteins fold to put hydrophobic (water-hating) amino acids in the middle and hydrophilic (water-loving) ones at each side of the membrane. Take these proteins out of the membrane and they tend to unravel.

Some proteins are pores, channels for specific molecules. Some are pumps; they use chemical energy to move molecules across the membrane. Some sense what is going on outside the cell and pass a signal to the inside. Huge enzyme complexes that transfer the chemical energy from food to chemicals such as adenosine triphosphate (ATP) are found in the mitochondria of our cells (see pages 12–13). The complexes only work when embedded in the membrane because they set up an electrochemical gradient across it.

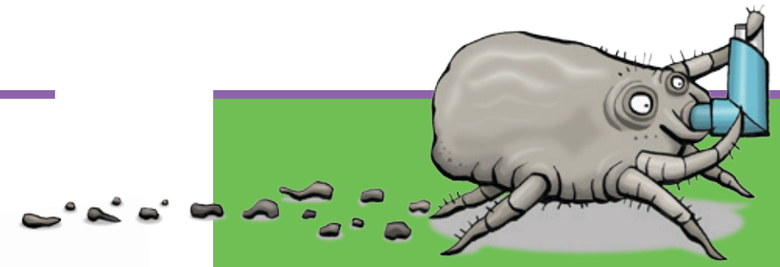
Researchers are exploring a large group of proteins known as G-protein-coupled receptors. These share a similar basic sequence, which crosses the membrane seven times, but are each tailored to a specific molecule.

The receptor reads an outside signal, usually a molecule that binds to the protein. This causes a change in shape that leads to the binding and activation of a previously inactive protein – a G protein – inside the cell. This basic system is very versatile and is involved in many things, including sight, taste and smell, and passing on the messages from hormones and neurotransmitters. About half of all drugs used in medicine act on G-protein-coupled receptors. The Nobel Prize in Chemistry for 2012 was awarded for research on these proteins.

▶ **MORE ONLINE: www.wellcome.ac.uk/bigpicture/proteins**

DEFENCE AND SURVIVAL

From antibodies to blood-clotting factors, proteins are vital for keeping organisms alive.



FAST FACT
Up to 85 per cent of people with asthma are allergic to house dust mites. Source: **www.ncbi.nlm.nih.gov/pmc/articles/PMC3381841/**

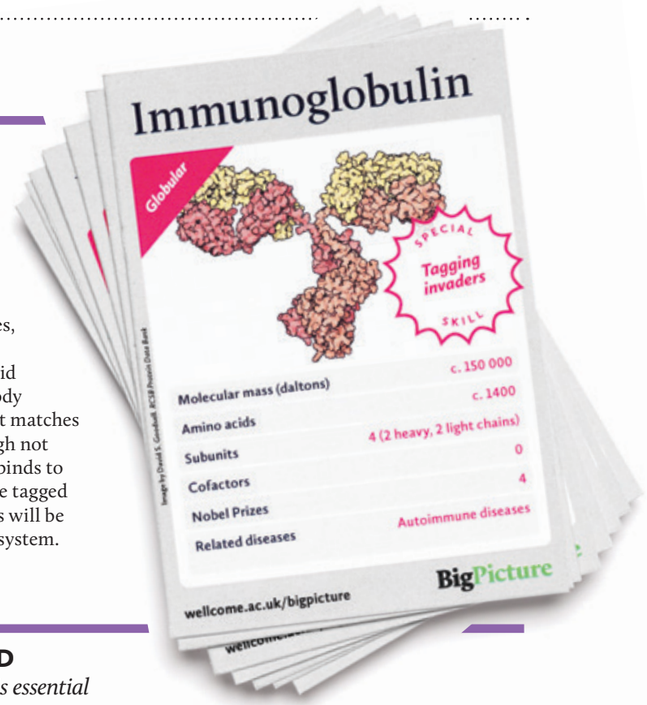
FOCUS PROTEIN: IMMUNOGLOBULIN

Binding to unwanted invaders

Antibodies or immunoglobulins (Ig for short) are globular proteins, each with the same four-chain structure – two heavy and two light chains. The antibody's four chains are arranged in a Y shape. At the end of the antibody arms are the antigen-binding sites, variable regions that differ in their amino acid sequence.

Antigens are molecules that can provoke an immune response. They are often proteins, and include parts of bacteria, viruses and cells from transplanted blood or organs. Your own cells carry 'self-antigens', which do not usually trigger an antibody response.

Each B lymphocyte produces a specific type of antibody. We can make as many as a hundred million antibodies, which means a hundred million different amino acid combinations. If an antibody encounters an antigen that matches it, it will bind to it, although not as precisely as an enzyme binds to its substrate. Once they are tagged by antibodies, the antigens will be destroyed by the immune system.



STEMMING THE FLOW

Proteins are vital for blood clotting

One of blood's amazing properties is that it contains a liquid toolkit that starts the repair of blood vessels if they spring a leak. A collection of soluble proteins is activated when tissue is damaged. These proteins unite to make an insoluble complex, which is the beginning of a blood clot.

When you cut yourself, you do not bleed for long. A cascade of reactions is triggered, which leads to the activation of the enzyme thrombin from its precursor protein prothrombin. Thrombin, in turn, converts the soluble protein fibrinogen into insoluble fibrin, which builds the scaffolding for a clot.

Poisonous snakes often harm their prey by interfering with blood clotting. Snakes produce more than 100 thrombin-like enzymes, which cause blood to coagulate inside the blood vessels.

PART OF THE FOLD

Correct protein folding is essential

Everything a protein does depends on its shape, which itself relies on the precise folding of the protein chain(s). There is one shape that has the lowest energy, which the protein will keep if it finds it. But that does not always happen easily. Some newly made protein chains need help from chaperone proteins to undo any misfolding as it happens.

When folding goes awry, the results are usually bad. Having the wrong shape may simply mean that a protein does not work properly. Others can lead to accumulated 'junk' that eventually kills cells. A new protein has to find the right shape among an astronomical number of possibilities. Some of the intermediate shapes between the unfolded chain and the working protein are 'stickier' than the desired end product and begin to clump together before folding is complete.

A famous example is the prion: prion proteins are harmless in their normally folded state but can refold to make a super-stable complex that clogs cells. This switch is irreversible because the diseased form of the prion collects with other prions and induces them to convert to the diseased form too.

Sometimes, as in the fatal Creutzfeldt-Jakob disease (CJD), the defect arises when a prion protein in its normal shape switches to a diseased form inside the patient's body. But prion disease can also be transmitted between people or even between different species, as discovered when people ate beef products from cows with bovine spongiform encephalopathy (BSE, or 'mad cow disease'). Starting in the mid-1990s, some people developed what is called variant CJD, thought to be transmitted by prions in the affected meat. In 2011, five deaths in the UK were caused by variant CJD.

Alzheimer's, Parkinson's and Huntington's disease are caused by misfolded proteins that clump together and cannot be disposed of normally. Parkinson's and Alzheimer's develop with age, either because the protein clumps grow larger or because the machinery that helps proteins fold properly gets less good at its job.

UNDER ATTACK

Scientists work to counteract some proteins' effects

Proteins and peptides can be used for attack – for example, in venoms such as bee and wasp stings and snake bites. Bee venom delivers a dose of melittin, a 26-amino-acid peptide that inhibits several transport proteins and enzymes as well as attacking cell membranes.

Researchers in the USA are hoping to use melittin to destroy HIV (human immunodeficiency virus). The toxin is loaded into carefully tailored nanoparticles, which have molecular 'bumpers' attached. This means that they cannot get close to human cells but can fuse with HIV particles, which are much smaller. A similar melittin-based system could also have uses in treating cancers.

Researchers are also looking for ways to block outside agents that trigger an overreaction from our immune system. Asthma attacks, for instance, are often triggered by proteins found in dust mite excrement. The main culprit is an enzyme that attacks the lining of the lungs. A drug in development is designed to block the enzyme action and could prevent asthma developing in those exposed to the protein.

Bee venom delivers a dose of melittin, a peptide that inhibits some proteins. *Shutterstock/Ilya Andriyanov*

USING ANTIBODIES

Exploring antibodies as medicine and in research

Antibodies are made by white blood cells called B lymphocytes. Each cell produces just one kind of antibody. If you can induce the cells to grow, they can give you pure antibodies. Researchers first did this 35 years ago by hybridising (joining together) mouse lymphocytes with cancer cells that grow indefinitely. The hybrid cells yield monoclonal antibodies (MAbs), which can be produced with endlessly different shapes.

Antibodies tagged with fluorescent dye enable scientists to locate target molecules under the microscope. This can tell you whether cells in a tissue are making a specific protein, for example, and even where in the cell the protein is found.

MAbs are also used in pregnancy test kits to detect hormones and to help diagnose conditions where particular proteins indicate something is amiss, such as after a heart attack.

Other medical uses include MAbs that block cell–surface receptors. For example, the drug Herceptin (trastuzumab) blocks a receptor found in some types of breast cancer and inhibits tumour growth.

DISCUSS

FREEZE!

Proteins stop fish from freezing

Louise Murray/Science Photo Library

Fish in the Antarctic live in salt water that can be below normal freezing point. If the water inside the fish froze then its volume would increase and the fishes' cells would burst, so they protect themselves from the cold with special glycopeptides – amino acid strings in which a threonine side chain has a sugar molecule attached. Any ice crystals that form become coated with this natural antifreeze and remain too small to cause damage.

Such natural antifreeze molecules could help to improve tissue preservation in medicine (e.g. in sperm banks or when donated organs have to be shipped for transplant in another hospital). They could even be applied in cryonics, where people pay to have their bodies – or sometimes just their heads – frozen after death, in the hope that one day medicine will be sufficiently advanced to bring them back to life.

Questions:

- Would you want your body to be frozen after you die? Why?
- What would be the consequences if this practice became routine?
- How are doctors using low temperatures? (Hint: start exploring this by searching for "therapeutic hypothermia" online.)

▶ **MORE ONLINE: www.wellcome.ac.uk/bigpicture/proteins**

SIGNALLING

Proteins – as cell receptors, enzymes, hormones and pheromones – are central to communication in living things.

Shutterstock / Irin-k

FAST FACT

When tomato plants are wounded or attacked by herbivores, they release an 18-amino-acid polypeptide called systemin into their circulation. This triggers the activation of genes for defence throughout the plant.
Source: **www.ncbi.nlm.nih.gov/pubmed/9891776**

FOCUS PROTEIN: INSULIN

Regulating glucose in the blood

Insulin is a small protein hormone that signals how much of the sugar glucose there is in the blood. It has also been central to the history of protein research. It was discovered in the 1920s, and it was quickly used to treat patients with diabetes. It was the first protein to be sequenced, the first to be chemically synthesised and the first human protein to be made in engineered bacteria.

It has just 51 amino acids, arranged in two chains linked by disulphide bonds. It begins life as a much larger protein, which helps the molecule fold into the right shape. Then a large fragment of the precursor, proinsulin, is snipped free by enzymes, leaving the small, soluble hormone protein free to do its job.

People with type 1 diabetes make too little or no insulin and are treated with the hormone. People with type 2 diabetes, which most often appears in later life, have lost some degree of response to insulin. Their treatment initially focuses on diet.

DISCUSS

GROWING UP

We all need growth hormone – but in the right amounts

Growth hormone is a small soluble protein made in the pituitary gland in the brain and released into the bloodstream. Like insulin and other peptide hormones, it works by triggering a 'second messenger', which is released inside a cell when the hormone binds to a receptor on the outside of the cell membrane. Steroid hormones are smaller, fat-soluble molecules that can pass through cell membranes and usually transmit their message directly.

Growth hormone stimulates cell division in tissues sensitive to it. Most obviously, it promotes bone growth, and too little or too much of it leads to extremes of stature. Children who don't make enough growth hormone can be given more until they reach an acceptable height. Like insulin, growth hormone has many other metabolic effects. Both of these hormones are now made by genetically engineered bacteria.

Humans naturally produce less growth hormone as they age. Some people think growth hormone can delay ageing, and some anti-ageing products such as face creams now include growth hormone. Some people go as far as injecting the hormone, either to slow ageing or to boost their fitness, even though it is not licensed for this kind of use in the UK.

In some countries outside of the European Union, cow growth hormone (bovine somatropin) is used to boost milk production in cows.

Questions

- What is an 'acceptable height' for children who require human growth hormone? Who should decide?
- What are the potential benefits and risks for someone injecting themselves with human growth hormone to slow down ageing?
- What are the arguments for and against the use of cow growth hormone in dairy farming?

PASS IT ON

Pheromones get the message across

Hormones carry messages between cells in the same organism. Pheromones carry messages between individuals of the same species. The same types of chemicals tend to be involved, including peptides and proteins, the latter most often as receptors.

Insects often use small, volatile molecules as pheromone messengers because they can travel relatively long distances in the air. Protein and peptide pheromones are much more common among bacteria, where they are effective messengers in solution, and pass between cells.

Bacteria release pheromones as an aid to conjugation (when bacterial cells link to transfer DNA), and many use the concentration of particular pheromones as an index of the local population density.

This is useful in quorum sensing, where a colony of bacteria behaves in a particular way if enough bacteria are nearby. For example, a bacterium that lives in marine creatures will make a glowing chemical only when individual bacteria have detected that there are enough other bacteria nearby for the emitted light to be visible.

SWITCHING SIGNALS

Kinase proteins control cell processes

Hormone systems often act through a sequence in which the hormone binds to its receptor on the outside of the cell to activate the enzyme inside the cell. This system allows a signal carried by small amounts of a hormone to be amplified inside the cell. Typically, the enzyme involved, a kinase, adds a small chemical group (a phosphate) onto another protein. Protein kinases regulate many interactions in cells. The insulin receptor, for example, operates by turning on a protein kinase when insulin binds.

BRAF is a human gene that contains the information to make a protein called BRAF. BRAF is an enzyme that regulates cell growth. To be active, the BRAF protein usually requires a signal from outside the cell. However, some mutations make it permanently active as a kinase, even without this signal.

Some inborn mutations in BRAF cause growth disorders. Some mutations, which can also arise in individual cells later in life, can lead to uncontrolled cell growth – cancer. The skin cancer melanoma is often associated with BRAF mutations, for example. Several chemicals that inhibit BRAF show promise as potential cancer treatments, but they will need to be tested in clinical trials before they can be used in hospitals.

FEELING STUFFED

Hormones influence our eating

Peptide hormones play an important part in bringing on both the pangs of hunger and the feeling of being comfortably full after a meal, but their role in appetite is not completely understood. Research suggests that receptors in the gut, closely related to taste receptors, register the presence of specific food chemicals and trigger or suppress hormone release.

One key messenger is the peptide hormone ghrelin, which stimulates cravings for high-calorie foods when it is released in the gut. Blocking the action of the hormone, even vaccinating against it, might prevent obesity. However, ghrelin has other roles in the body, such as combating inflammation in the gut, and is implicated in our response to stress.

Food intake is too important to be left to a single hormone, and several other messengers in the gut influence the processing and absorption of food. For example, there are receptors and transporter proteins in the gut for several different amino acids and peptides, and for glucose, and each kind can affect the other.

Shutterstock/Valertyn Volkov

MAN THE PUMPS

Drugs can overcome mutations in proteins

Diseases can occur when membrane proteins function incorrectly or not at all, and drugs often work by affecting how these proteins function.

For example, researchers found that diabetes in some newborn babies was caused by mutations in a potassium ion channel that affected the secretion of insulin from cells in the pancreas.

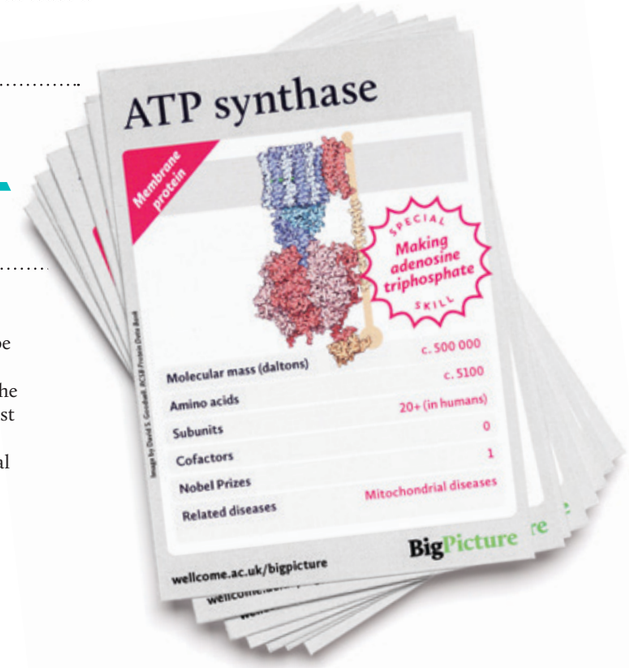
In affected babies, the potassium channels are stuck open, but researchers found a drug that can close the channels and trigger the release of insulin.

The drug can be given as a tablet, which means that children with this form of the disease are spared the regular insulin injections used to treat diabetes.

▶ **MORE ONLINE: www.wellcome.ac.uk/bigpicture/proteins**

CATALYSIS

Enzymes are proteins that increase the rate of reactions, often by at least a million times that of the uncatalysed reaction.



FOCUS PROTEIN: ATP SYNTHASE

Capturing energy for our cells

Calling adenosine triphosphate (ATP) synthase an enzyme hardly does it justice. True, it makes ATP, but the protein is an impressive nanoscale machine – a complex of proteins consisting of a transmembrane pump and two linked motors, which rotate.

Different forms of ATP synthase are found in bacteria and in the membranes of mitochondria and plant chloroplasts, but the enzyme's general mechanism is conserved across organisms. As protons cross the membrane, down a concentration gradient, one motor turns, driving an axle that turns the other and producing ATP in the process. The axle driving the ATP-making enzyme rotates 150 times a second. The cleverest part is that these motors can be thrown into reverse, and ATP can be hydrolysed to provide the energy to pump protons against an electrochemical gradient.

This protein is fundamental to living things. A person makes and recycles roughly their body weight in ATP every day.

LIFE ON THE EDGE

Meet nature's extremophiles

Proteins are generally sensitive to heat, but in recent decades bacteria and other organisms that survive in extreme conditions have been found. These 'extremophiles' need specially adapted enzymes so they can carry out essential reactions. Thermophiles thrive in high temperatures. One example is the bacterium *Thermus aquaticus*, first isolated from the scalding hot springs of Yellowstone Park. Its enzymes work normally at the temperature of a hot cup of tea.

The polymerase chain reaction (PCR), which is widely used in laboratories to amplify small samples of DNA, uses cycles of heating and cooling to separate and rejoin DNA double helices. The synthesis of new DNA, which produces the amplification, needs a DNA polymerase enzyme that can withstand high temperatures. The answer was to use Taq polymerase from *Thermus aquaticus*.

A microscopic animal called the water bear (*Milnesium tardigradum*, right) can withstand prolonged drying out and is a psychrophile – it can withstand the freezing temperatures of the Antarctic. Experiments by NASA showed it is also able to tolerate the high vacuum and intense radiation of space. The water bears survive thanks to an unusually large repertoire of heat shock proteins – so named because they were first discovered as part of cells' response to heat stress. Most organisms produce some of these, and they have a general role in protecting other proteins. Many are chaperone proteins, which help to stabilise newly formed protein chains.

Closer to home, our stomach contents are kept at a pH low enough to kill most cells and denature enzymes, but our digestive proteases operate happily in this acidic soup.

Eye of Science/Science Photo Library

BREAK IT DOWN!

The proteins that dispose of proteins

Cells make proteins, but they must also dispose of the unwanted, damaged or misfolded ones. In eukaryotic organisms, some protein degradation happens in special bags of enzymes called lysosomes inside the cells, and some in a big protein complex that floats free in the cell, the proteasome. The proteasome stops proteases attacking everything in the cell by containing them in a protein assembly.

The proteins destined for destruction are tagged with a small protein named ubiquitin, which is found in all eukaryotic cells and has an identical sequence in all animal species. Enzymes recognise proteins that are no longer required and tag them.

There is also a more drastic process of self-digestion: programmed cell death, or apoptosis. This involves the activation of a whole set of enzymes, mainly proteases, that degrade large molecules and destroy the structure inside a cell. Apoptosis is triggered by various kinds of cell damage, as cells can be sacrificed for the greater good of the organism. It also occurs in development when there is large-scale cell loss (e.g. when the webbing between a growing fetus's fingers disappears).

FAST FACT

Alcohol is sometimes given to patients with antifreeze (methanol) poisoning, as it competes with the enzymes that break down methanol into toxic products that include methanoate. Source: **www.methanol.org**

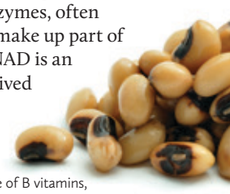
CUNNING CATALYSTS

Enzymes are proteins

Enzymes, like inorganic chemical catalysts, cannot make new reactions happen, but they speed them up enormously by lowering the activation energy for the reaction. Generally, enzymes are globular proteins, and they need the right conditions to do their job. Substrate–enzyme binding often depends on weak electrostatic forces and is easily disrupted by changes in acidity (pH). Heat denatures proteins and destroys enzyme activity.

Competitive inhibitors are molecules that have a similar shape to the enzyme's substrate, but do not react and instead block the active site. These competitive inhibitors can make good drugs – and poisons.

Many enzymes need a non-protein component called a cofactor to work. Some contain a metal atom held inside a stable chemical structure, such as haem in cytochrome 450, an enzyme that detoxifies chemicals in the liver. This is why we need traces of metals such as iron, magnesium, copper and zinc in our diet. Organic cofactors, known as coenzymes, often come from vitamins and make up part of the enzyme's active site. NAD is an example of a cofactor, derived from niacin (vitamin B3).



Black-eyed beans are a good source of B vitamins, including thiamin, niacin and riboflavin. *iStock*

GROWING OLD TOO SOON

Enzymes are involved in ageing

Enzymes that are inactive, or not active enough, are among many contributors to human ageing. Progeria is a very rare exaggerated form of ageing. It is seen in children with inadequate supplies of lamin, a fibrous protein that is vital for maintaining the structure of the cell nucleus. Patients typically suffer hair loss, joint problems and heart disease, and usually die in their mid-teens.

A major cause of progeria is a defect in a protease that completes the production of lamin from its precursor, prolamin. The protease, ZMPSTE24, is a complex transmembrane protein. In 2013 a team of X-ray crystallographers solved its 3D structure, explaining how several mutations disable the enzyme and bring on the symptoms of one type of progeria. Understanding more about this unusual protein structure may eventually help in the development of treatment for progeria and also explain the more gradual deterioration seen in normal ageing.

DISCUSS

WELL DIGESTED

Digestive enzymes can be useful

We make proteins by breaking down the ones we eat, then building new ones from their component amino acids. This breaking down is digestion, and lots of enzymes contribute. Proteases, for instance, hydrolyse (break) the peptide bonds in protein.

Some proteases are very specific and do more than food digestion. Several viruses, including HIV and poliovirus, use some of their proteases to produce finished protein products from larger precursor polypeptides. Insulin, as mentioned on page 10, is produced in the same way.

Digestive enzymes are useful in industry. Researchers have discovered enzymes in bacteria that can digest wood to produce liquid biofuel. Biofuels are fuels made from living matter, such as trees or cereal crops. At its most efficient, biofuel is carbon neutral because the carbon dioxide released when the fuel burns was absorbed from the atmosphere relatively recently, during the life of the plant.

In theory, using the woody parts of plants and crop waste would enable biofuel to be produced without competing with food production – and reduce carbon dioxide emissions by being used in place of fossil fuels. However, the potential impact on forests of large-scale biofuel production remains to be seen.

Questions:

- Describe three other ways that enzymes are used in industrial settings.
- How should we decide how much land to use for biofuels and how much to use for food production?

▶ **MORE ONLINE: www.wellcome.ac.uk/bigpicture/proteins**

REAL VOICES

Three people tell us about the part proteins play in their lives.

JACK ANDRAKA

US high school student and scientist

What do you do?
I'm a high school student and the inventor of a test to detect pancreatic cancer.

How does your test work?
I've created a novel paper sensor made from ordinary filter paper, single-walked carbon nanotubes and an antibody to mesothelin, a protein biomarker for pancreatic, ovarian and lung cancers. I dipped the filter paper into a mixture of the antibody and nanotubes, let it dry, and repeated until there was a coating on the paper. I then measured the conductivity. After mesothelin was applied to the sensor, the mesothelin bonded with the antibody and pushed the nanotubes apart. This changed the conductivity and could be measured with an ohmmeter that measures electrical resistance.

Why pancreatic cancer?
When I was in middle school, a close family friend passed away from pancreatic cancer. I didn't even know what a pancreas was, so I turned to the Internet to find out. The statistics I found shocked me, and I was determined to find a better way of diagnosing the disease so people could have the cancer detected earlier when they would have a better chance of survival.

What was the best part of making the test?
Working in the lab and learning from the scientists there. The process of science is the most fun part – just testing your hypothesis and seeing where it leads you.

When might the test be available?
Right now I'm in talks with biotechnology companies to get the strip made more quickly and uniformly so it can get to clinical trials. It takes a lot longer to get from 'proof of concept' to a finished product than I imagined!

What are you working on now?
I want to diagnose a variety of diseases easily, quickly and economically. I also want to develop my sensor to test more diseases. I'm a junior in high school so have two years before college. This year will be busy because I'm taking a lot of advanced classes, taking important exams, researching my projects, travelling and speaking.

What's the best advice you have?
Read widely and brainstorm a lot! The best advice I've been given is to patent your idea before you speak about it publicly. If a 15-year-old who didn't even know what a pancreas was can create a sensor to detect cancer using the Internet, just imagine what you can do! We need to remove obstacles to learning by having open access to journal articles and scientific knowledge so kids like me can create and innovate.

Find out more at
www.jackandraka.net

SAMANTHA RENKE

Actress and public relations professional

What do you do?
I used to be a language teacher, but I am now working in marketing and PR. I'm also doing some acting – I'm quite busy! I'm 27 and currently living in London.

What is brittle bone disease?
It's a genetic disorder that affects type I collagen in the body and is also known as osteogenesis imperfecta. There is a lot of collagen in our skeleton so it causes us to have very low bone density and fragile bones.

Owing to multiple fractures, people with the condition usually have stunted growth. This happens because when you're constantly fracturing, the body needs to attend to the fracture before it can continue to grow. The new bone that grows back is very weak and can also be deformed, causing bowing of the arms and legs. Usually we have scoliosis, which is a curvature of the spine. That can push on our heart and lungs.

How does it affect you?
I've got type III osteogenesis imperfecta, which means that I'm a full-time wheelchair user. I've had approximately 200 breaks in my life. They actually started in the womb, when my mum was carrying me. When I was a baby I would fracture up to a few times a week. There's no indication when I'm going to break: I've been tipped out of my chair onto a pavement and nothing's happened to me, but I've rolled over in bed and snapped my collarbone.

Are there any treatments?
There is no known cure, but there are a few drugs (bisphosphonates) that can be taken to increase bone density. Curvature of the spine can often be rectified by putting rods into the back, which I've had done. I've also got telescopic rods in my legs to support them and to correct any bowing.

What's the most difficult thing?
Analysing everything I do and reducing all the risks. If I'm going out for drinks with friends, I have to think: how am I going to get there? What happens if they don't have a disabled toilet? What happens if there is a flight of stairs? So I do have to do a lot of planning for even the simplest of activities.

I'm quite eager to make sure that people view disabled people as integral to society. I've always been very positive and achieved a lot in my life – in spite of the fact that I've had to battle a lot due to my health, and because we don't live in a world that is designed for disabled people.

Find out more at
www.brittlebone.org

Read an extended version of some of these interviews at **www.wellcome.ac.uk/bigpicture/proteins**

HANNAH POWELL

Olympic weightlifter

How did you start weightlifting?
I started when I was 11, at secondary school. I hold a few British records for my age category and for my weight category, and I've competed internationally for Great Britain and for England.

How do people react?
Most of the time, the reaction is shock, mainly because I'm only 4' 8". I also often get asked if weightlifting is the reason I'm so small, but it's not. My height's an advantage. Usually the best shape for weightlifters is short everything: short arms, short legs and short body.

Which category are you in?
I'm in the lightest bodyweight category (48 kg), but I'm light for my class at 45 kg. Usually girls in this class train around 50 kg and then lose the last 2 kg over a couple of weeks to compete. The heavier you are, the more you lift, so if you're training heavy then you're training better. I'm constantly trying to put weight on.

Do you eat lots of protein?
A mistake a lot of people make when weight training is to overload on protein thinking that it's going to help them build massive muscles, but your body is only going to use so much. The thing I eat most of is complex carbohydrates, as that's what's going to help me put on weight, but protein straight after training is what helps you build the muscle once you've broken it down in training.

Chocolate is my weakness. I'm not really bothered about junk food, but every single day I find myself thinking 'I really want some chocolate'!

How often do you train?
I train about five times a week. I'm not funded [by British Weight Lifting] at the moment, so I work full time as a classroom assistant at a primary school. Going from being funded and able to train twice a day to working full time and trying to squeeze training in around work is quite hard – but I choose to do it.

Is it a male-dominated sport?
Yes. Women didn't compete in the Olympics until 2000. In the 14 years since, though, the standard of female lifting has rocketed. There are women out there who are outlifting men. 2012 has opened people's eyes to new sports.

What's next for you?
The 2014 Commonwealth Games will be the biggest chance I've ever had to perform on the international stage, so I'm working really hard and trying to keep things quiet.

Find out more at
www. britishweightlifting.org

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