

Secret Language of Cells

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They're all talking about you. Billions of tiny voices whispering day and night, commenting on everything you say and do, controlling your every move. But there's no need to get paranoid – these ceaseless conversations are being held between the cells of your own body as they work as a team to keep you alive. CELLULAR CHATTER is essential for all multicellular animals. Without it, the coordination and cooperation of the millions of cells in our bodies would break down. It would be like trying to run a country with no telephones, post or Internet, where the people were unable to speak.

Everything you do relies on the ability of cells to talk to each other. Communication is needed in a developing embryo to tell cells where to go, what to become and when to divide. Signals between cells orchestrate your appetite, movement and behaviour. When communications fail, the consequences can be devastating, from birth defects to autoimmune disease and cancer.

So how do cells communicate? Although each is contained within its own plasma membrane, they are not shut off from one another. Cells in most tissues are connected by tiny "tunnels" called gap junctions, which are essentially cylindrical membrane proteins with channels running through them. These are particularly important in heart muscle, as they allow charged ions to carry electrical impulses through the cells so that they contract in unison. But cells need an efficient way of sending and receiving messages over much greater distances. To do this, they use signal transduction mechanisms to receive and interpret chemical messages. Although these come in a multitude of forms, they all share the same basic logic.

A molecular message, or ligand, binds to a receiver protein known as a receptor. The binding of the ligand causes the receptor to change shape or cluster with other receptors. This sets off a cascade of protein interactions inside the cell, and either results in the activation/deactivation of key enzymes, or the switching on/off of transcription factors – proteins that regulate the expression of genes. It is the activity of these enzymes or the expression of these target genes that alters the behaviour of the cell in response to the signal.

But this is just a snapshot of what happens when a single signal is received. In reality, cells are constantly bombarded with hundreds of different signals, and are continuously adapting and responding to their environment. Each is equipped with its own set of receptors and signals that meet its specialised role, allowing it to respond to some signals and ignore all the rest. This is just as well, because being a cell in a multicellular organism is rather like standing at the bar in a crowded, noisy pub. If you didn't have the ability to focus your attention, you wouldn't hear what drink your friend was asking you to buy. Her voice would be drowned out by the hundreds of others clamouring for attention.

The bar analogy also illustrates the different sorts of signals that can be used. Some carry messages over long distances – like your friend standing on a chair and bellowing across the room that she wants you to get her a pint of beer. In the body, these endocrine signals are normally released into the blood, and include hormones such as the sex hormones oestrogen and testosterone; insulin to regulate blood sugar; and adrenaline to ready an animal for fighting or running away.

In contrast, a tall dark stranger whispering into your ear that they would like a vodka Martini, shaken not stirred, would be an example of paracrine signalling. These signals are sent over very short distances and include growth factors, which are involved in wound healing and cell division, and neurotransmitters, which convey signals between nerve cells.

After all this time in the pub, you're probably a bit squiffy and keep telling yourself to go to the bar for glasses of water to sober up a bit. This would be autocrine signalling, where a cell actually sends a signal to itself. Immune cells called T cells use it to help them divide when faced

with a foreign protein, so that they can rapidly ramp up the body's defences. But cancer cells can also use autocrine signalling to let them proliferate willy-nilly. Some breast cancers produce oestrogen to drive rapid cell division. The breast cancer drug tamoxifen blocks the receptor for oestrogen in an attempt to slow the cancerous cells down.

There are hundreds of different signalling molecules, but to make the mindboggling complexity a bit easier to deal with they can be grouped into five families: steroid hormones, dissolved gases, neurotransmitters, peptides and eicosanoids.

HOT GOSSIP

Water-hating sex hormones

The sex hormones oestrogen, progesterone and testosterone are members of the steroid hormone family, which also includes the stress hormone, cortisol. One unusual feature of these hormones is that their receptors aren't found on the surface of cells. Most signalling molecules are water-loving or hydrophilic, so they are unable to pass through the fatty cell membrane (which is why they need a receptor to pass on their message). But steroid hormones are small, water-hating or hydro-phobic molecules that can easily slip through the membrane. Once inside the cell, they bind to their intracellular, internal receptors. These are in fact transcription factors, and binding makes them change shape and switch genes on or off.

One of the biggest surprises for cell signalling researchers was the discovery that dissolved gases can act as messages in the body. Nitric oxide (NO) is probably best known for creating acid rain and as a toxic component of cigarette smoke. But scientists have found that it also works as a paracrine and autocrine signal. NO is produced in the lining of the arteries and diffuses to the surrounding muscle, causing it to relax and the blood vessels to dilate. This is why nitroglycerin, most famous as the high-explosive used in dynamite, is given to patients with heart disease. In the body it's converted to NO, which dilates blood vessels and so reduces high blood pressure and increases blood flow. NO also regulates blood flow in the sex organs (see Box 1).

Neurotransmitters carry signals between neurons, or between neurons and other types of target such as muscle cells. They are small molecules that travel across the tiny gaps, or synapses, between neurons and their targets. Neurotransmitters are released into the synapse when a nerve impulse arrives at the end of the neuron. Because they are hydrophilic and can't cross the cell membrane by themselves, neurotransmitters need to bind to cell surface receptors. Some of these transduce a signal within the cell to regulate the activity of ion channels, which control the flow of ions across the membrane in the transmission of nerve impulses. But many of the receptors are ligand-gated ion channels that change shape when the neurotransmitter binds. One such is the acetylcholine receptor in skeletal muscle cells. When the neurotransmitter acetylcholine binds to it, this opens up the channel, allowing sodium ions to flood into the cell. The resulting "action potential" – a difference in electric charge across the membrane – triggers the release of calcium ions from a store inside the cell and causes the muscle cell to contract.

Neurotransmitters also play a key role in the brain. Serotonin helps determine mood, and low levels can lead to depression. The clubbing drug Ecstasy (MDMA) works by boosting levels of serotonin. This gives users their warm high, but also causes side-effects. For example, high levels of serotonin in the hypothalamus stop the kidneys excreting fluid, which is why users can die from drinking too much water. Many researchers believe that long-term Ecstasy use damages the body's ability to produce serotonin.

The largest family of signalling molecules are peptides, which consist of amino acids linked in a chain. Peptides range in size from a few amino acids to more than a hundred. They include peptide hormones, such as insulin and growth factors like platelet-derived growth factor, which is involved in wound healing. Many growth factors regulate development, controlling

cell division and telling cells what to become. Cytokines such as interferons and interleukins are a good example (see Inside Science, No. 12). They regulate the development and differentiation of immune cells such as T and B lymphocytes. Immune cells also release cytokines that coordinate the body's response to infection. The loss of helper T cells due to HIV infection is behind the devastating effects on patients' immune defences.

The last class of signals are the eicosanoids, which include the prosta-glandins. These are fatty molecules, or lipids, that act locally to promote inflammation, blood clotting and smooth muscle contraction. Aspirin blocks the production of eicosanoids, which is why it can be used both to reduce inflammation and reduce the risk of strokes.

Of course, cell communication isn't confined to animals. Plant cells need to communicate with each other, and even single-celled animals such as yeasts send messages to other cells. Much research interest, however, is focused on the role that signalling plays in human diseases such as cancer, obesity and diabetes. Developmental biology is another major growth area. A key goal is to piece together how cells in a developing embryo communicate, what they are saying and what happens when communication breaks down.

You might not think you have much in common with flies or worms, but scientists use animals such as the fruit fly *Drosophila melanogaster* and the worm *Caenorhabditis elegans* to eavesdrop on signalling pathways chattering away inside the embryo. Many of these have been conserved over evolutionary time, so we share many of them with lower organisms. One example is the signalling molecule hedgehog, so-called because fly embryos that lack it are covered with tiny bristles. In flies, hedgehog tells cells in the developing wings where and what they are – it "patterns" the tissue. In humans, similar molecules are involved in limb development, and also cell division. A form of human skin cancer, basal cell carcinoma, arises when the receptor for the human version of hedgehog is faulty.

So how do signals affect cells in the embryo? As mentioned before, they can switch on transcription factors that alter a cell's behaviour. An embryo starts off as a collection of very similar cells, each containing the same genes. To develop specialised tissue, such as muscle or blood, different sets of genes need to be switched on or off (see Inside Science, No. 40). Cell signalling is central to this process of differentiation, and when it goes wrong development is severely affected.

A stark example is what happens when signalling that regulates limb development is disrupted by the drug thalidomide. Thalidomide was prescribed to pregnant women in the 1960s to combat morning sickness. But it was soon clear it could have a devastating effect on the embryo. Many babies were born with shortened limbs – the worst cases had hands and feet attached directly to the trunk.

SIGNAL FAILURE IN THE WOMB

The story of thalidomide

Normally, arms and legs develop from limb buds that grow out of the embryo (see Figure 3). A strip of tissue called the apical ectodermal ridge lies on the end of the bud. It tells nearby cells how far away from the main part of the body they are by sending out signals of fibroblast growth factors (FGFs). Normally, cells in the "progress zone" at the end of the bud are constantly dividing. As division proceeds, older cells get farther and farther from the apical ectodermal ridge. The FGFs only diffuse a short distance, and the cells in the progress zone differentiate according to how long they have been receiving the signals. Cells that receive FGF signals for the longest, for example, become hands or feet.

One theory suggests that thalidomide halts cell division in the progress zone, so all the cells receive FGFs for a long time and differentiate as if they were located at the end of a completed limb. So they become hands or feet.

Differentiation is also the key to understanding cancer (see Inside Science, No. 32). Cancer arises when cells begin to revert to a less specialised, less differentiated state, allowing them to divide and spread. Several controls need to be disrupted before a cell becomes truly cancerous and invasive. But one of the key steps is the loss of control over cell division. This can happen in many ways, but often a cell acquires a mutation that damages one of the proteins involved in signal transduction. One example involves a protein called Ras that triggers cell division. Ras is normally only activated when a cell receives a signal to divide from certain growth factors. But in many cancers, a faulty Ras protein stays permanently switched on, forcing the cell to keep dividing.

Another way that tumours hijack cell signalling is by conning the body into providing them with a blood supply. A tumour can only grow so large before the cells at its core become starved of nutrients and oxygen. To keep growing, it needs to get a better blood supply and sends out signals, including vascular endothelial growth factor (VEGF), to encourage the growth of new blood vessels. Scientists are studying communications between tumours and their environment in the hope of developing new drugs to block these signals and so suffocate tumours.

Death is another focus of intensive research. As you read this, thousands of your cells are killing themselves. Don't panic – they're doing it for your own good. Cell suicide, also called programmed cell death or apoptosis, is essential for life. When you were growing inside your mother's womb, for example, apoptosis pruned away excess neurons in your developing brain and dissolved the webs of skin between your growing fingers and toes. Now it helps to safeguard you against autoimmune disease and cancer, and fend off viral infections.

Apoptosis prevents cancer by keeping a tight rein on cell division. One way the body does this is by forcing cells in tissues such as the skin to be reliant on signals from their neighbours and immediate environment to stay alive. If these signals are not getting through (for example, if a cell starts to move out of its correct environment), an auto-destruct program is activated and the cell commits suicide.

Another key role for apoptosis is destroying infected cells. Killer T cells, the body's assassins, track down and kill these cells by instructing them to top themselves. Most cells in the body have a "death receptor" called CD95 on their surface that acts as a receiver for this death command. If any become infected, with a virus for example, the immune system can use CD95 to destroy them.

Patrolling killer T cells keep tabs on other cells by constantly sampling protein fragments, or antigens, that they hold out for inspection on their surfaces in conjunction with major histocompatibility complex or MHC molecules (see Inside Science, No. 143). If a cell is infected with a virus, fragments of viral protein appear on its surface and are recognised as foreign. The T cell also carries a cell-surface molecule called CD95L. When it moves in for the kill, its CD95L molecules stick to CD95 receptors on the infected cells. This sets off a cascade of protein interactions within the cell, resulting in enzymes called caspases being switched on. Caspases work like chainsaws, chopping up key proteins and activating other enzymes that carve up the doomed cell's DNA. Fragments of the dead cell are gobbled up or "phagocytosed" by its neighbours or other immune cells.

Apoptosis is a prime example of the body protecting itself from ill health, but there are other times when we're our own worst enemy. To put it plainly, we eat too much. Over half the population of Europe and the US are either overweight or obese. Things have got so bad that some scientists think obesity is now the biggest health problem facing the developed world (see Box 2). Invent a pill that shrinks expanding waistlines and you'll be rich beyond your wildest dreams. But dream on – the signalling mechanisms that control a person's weight and appetite are so complex and finely balanced that there is unlikely to be a single magic bullet that busts the bulge.

One signal that plays a key role in how our bodies store fat is a hormone called leptin. Secreted by fat cells, or adipocytes, the amount of leptin in the bloodstream depends on the amount of body fat a person has stored. Leptin levels also rise after a meal and then gradually drop, prompting the person to eat again.

Many cells in the body carry receptors for leptin, including those in an area of the brain called the hypothalamus that controls appetite and eating behaviour. What's more, leptin has a say in several other important areas of the body, including the immune and reproductive systems. When levels drop too low, the body thinks it is starving and cuts back on anything that will drain its resources further, such as the immune system. In women, the menstrual cycle may cease completely. This is why women with very low amounts of body fat, such as ballerinas and marathon runners, often don't have periods.

Unfortunately, dishing out leptin to obese patients doesn't work. One reason may be that their leptin receptors or other components of their signalling pathways aren't working properly, partly as a result of genetic faults. And if their cells can't transduce the signal, it doesn't matter how much leptin is around. The genetic factors involved in predisposing people to obesity are likely to be many – it is a polygenic trait (see *Inside Science*, No. 138).

Now that the Human Genome Project has completed a working draft, tracking down signalling genes like these will be much easier. But scientists are well aware that the signalling pathways they have worked out so far are just the beginning – more and more evidence is emerging that these pathways cross and feed into each other. Unravelling all this signalling spaghetti is the next great challenge for scientists trying to translate the secret language of cell communication.

Box 1: Is that a gun in your pocket?

Viagra, the famous blue pill that has restored many a flagging sex life was discovered by accident by chemists at the drugs company Pfizer. They were testing a compound called sildenafil citrate on men as a possible heart drug, and some of the men reported that it had cured their inability to get an erection.

Impotence, or erectile dysfunction, affects up to 30 million men worldwide. Normally, the spongy erectile tissue in the penis fills with blood during arousal. But for this to happen, the smooth muscle surrounding the blood vessels in this tissue has to relax, allowing blood to flow in. When a man is aroused, nerve endings in his penis release nitric oxide, which diffuses into the smooth muscle cells through their membrane. Inside the cells, it increases the levels of a messenger molecule called cyclic GMP, the signal for the muscle to relax.

However, there has to be a way of switching this process off, otherwise men would walk around with permanent erections. This is where an enzyme called type-5 phosphodiesterase comes in. It lops a bit off the cyclic GMP molecule, inactivating it and allowing the penis to become flaccid again. Viagra works by blocking the activity of type-5 phosphodiesterase, maximising the effect of NO.

Box 2: Piling on the pounds can give you diabetes

Most people have heard of the complications of obesity, such as heart disease and strokes. But few are aware that being obese can also give you a form of diabetes.

Type 2 diabetes, as it is called, is most likely to strike in adulthood. Excess fat makes the body unable to respond to insulin, even though the pancreas can still make it (by contrast, type 1 diabetes usually begins in childhood and results from the insulin-producing cells of the pancreas being destroyed by the immune system).

How does fat interfere with insulin? In obese people, especially those with excess upper body fat, the breakdown of fat occurs at a faster rate. This results in high levels of fatty acids in the bloodstream, which interfere with the ability of the liver and skeletal muscles to respond to insulin. The upshot is that the tissues behave as if insulin levels were low.

Normally, insulin signals to the muscles and liver to snap up blood glucose and store it. But in obese patients, the liver keeps making glucose, and the muscles don't absorb glucose after a meal. Initially, the pancreas can compensate by churning out more insulin. But as levels of fatty acids rise, the pancreas can no longer compensate, resulting in dangerously high blood glucose levels or hyperglycaemia.

Patients with type 2 diabetes can be treated with drugs and are advised to lose weight.

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