colleagues tackled only one particular facet of atherosclerosis. In reality, many factors — both genetic and environmental — are likely to contribute to the disease. Not least, it can occur in the absence of raised levels of LDL cholesterol. A crucial question, then, is whether the interaction between apoB100 and proteoglycan is a general initiating mechanism for atherosclerosis, and it would be instructive to test its contribution to atherosclerosis induced by alterations in immune and inflammatory status. One approach would be to compare the susceptibility to atherosclerosis of normal and mutant human apoB100 transgenic mice cross-bred with mouse models of atherosclerosis caused by inflammation[7].

Skålén *et al.*[1] also show that other apolipoproteins, such as apoE, which is found in triglyceride-rich and remnant lipoproteins, can substitute for apoB100 in mediating the retention of lipoproteins in the arterial wall. Increased levels of triglyceride-rich remnant lipoproteins are often found in the serum of patients suffering from insulin resistance and type II diabetes, as well as in people carrying particular variants of apoE. In such individuals, it could be that the interaction between apoE and proteoglycans is the greater contributor to the initiation of atherosclerosis.

The findings of Skålén *et al.* illuminate one molecular basis for lipoprotein retention in the arterial wall. But other mechanisms of atherogenesis — which might or might not depend on lipoprotein retention — could also be operating at the same time. Even given similar levels of LDL cholesterol, not every person who develops atherosclerosis does so to the same extent. Moreover, in a given individual, atherosclerotic plaques do not develop at an equal rate and are not evenly distributed throughout the vasculature. Contributing factors might include regional disturbances of blood flow or alterations in proteoglycan structure. The raised LDL concentrations due to overexpression of apoB100 in Skålén and colleagues' transgenic mice might induce an inflammatory response, resulting in increased proteoglycan expression and congregation of white blood cells at susceptible locations. Local inflammation at such sites would intensify the modification of LDL by activated cells of the arterial wall.

Whether lipoprotein retention and modification are involved in the ensuing course of atherosclerosis also remains an open question. Atherosclerotic plaques did form in mice with proteoglycan-binding-deficient human apoB100, albeit later than in mice expressing the normal form, which would seem to show that factors other than direct LDL retention by proteoglycans dominate after atherogenesis has been initiated. A major contributory factor may be lipoprotein lipase, an enzyme that is secreted by macrophages in the artery wall and provides a high-affinity bridge between lipoproteins and proteoglycans[8]. It will be interesting to compare plaque development in normal and mutant apoB100 transgenic mice over a longer period. And are human subjects with mutations in the proteoglycan-interacting domain of apoB protected from atherosclerosis? It could be productive to search for these mutations in healthy octogenarians.

Even though it is clear that decreasing the concentration of cholesterol reduces the incidence and degree of atherosclerosis, most patients suffering from the disease still die from cardiovascular complications. Therapies that act directly on the arterial wall are needed, and Skålén and colleagues' results point to potential targets. One might consider, for example, using proteoglycan mimics that interfere with apoB100 retention in the wall. But great care and precision would be needed. Proteoglycans have other physiological functions that might be compromised by such an approach, and different proteoglycans might have different effects on lipoprotein retention and thus in atherogenesis[9]. A complementary strategy would involve modulating the ability of LDLs to interact with proteoglycans by altering their composition and particle size. Given these new findings, measurements of the ability of LDL to bind to proteoglycans might produce a helpful diagnostic test, and decreasing the strength of the interaction would be a reasonable therapeutic approach. ■

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Nanotechnology

Electronics and the single atom

Silvano De Franceschi and Leo Kouwenhoven

The invention of semiconductor transistors in the 1940s revolutionized electronic circuitry. In the new world of 'nanoelectronics', a transistor whose active component is a single atom has now been demonstrated.

Nanotechnologists are seeking to build nanometre-scale electronic devices in which the functional unit is a single molecule or atom[1]. Carbon nanotubes have proved particularly useful as molecular 'wires'[2] in this quest, thanks to their long lengths (by nanotechnology standards at least) of several micrometres. So could it be possible to wire up a short molecule, or even a single atom, to create a nanoscale transistor? The experiments reported by Park *et al.*[3] and Liang *et al.*[4] (on page 722 and page 725 of this issue) give a positive answer.

Trapping a molecule between two metal electrodes to make such a transistor is a tough technological challenge[1,3–7]. First, the molecule needs suitable terminations that reliably bind it chemically to the two electrodes, bridging the gap between them. Conventional lithographic techniques by which the electrode structure might be assembled have a resolution, at best, of around 10 nm — yet the electrodes would need to be just 1 nm apart. The two groups[3,4] have used the unconventional combination of electron-beam lithography and electromigration to reach this 1-nm scale. Still, the entrapment of a single molecule in the electrode gap is an occasional, lucky event. Moreover, at present there is no viable imaging technique for directly confirming successful trapping. Yet the presence of one, and only one, molecule can be indirectly established from its conduction properties.

The molecules used by Park *et al.* and Liang *et al.* in their ultra-small transistors are organic complexes that contain one[3] or two[4] atoms of a transition metal. The metal atoms, cobalt[3] and di-vanadium[4], form the active region of the device, whereas the organic molecule serves as mechanical support and provides the connection to the metal electrodes. Both experiments demonstrate transistor operation based on a tunable flow of electrons through the metal atom. (Although this simple picture is largely correct, the properties of the metal atom are strongly affected by the presence of the organic molecule.)

The current through an electronic transistor can be turned on and off by changing the voltage on a gate electrode. In the 'on' state, current is carried by a large number of electrons, with typically a billion passing per second — the large number is necessary to obtain a measurable current. In a commercial silicon transistor, electrons move independently of each other by diffusive motion from the 'source' to the 'drain' terminal. Although the motion of an individual electron cannot

be predicted, the average motion of a large number of electrons can, resulting in well-defined transistor operation.

How do electrons flow through a single-molecule transistor? The answer is by a simple fundamental process. The repulsive Coulomb interaction between electrons means that there is an energy cost in adding an extra electron to any object of small dimensions (this same energy cost is in part responsible for the ionization and affinity energies in an atom). In a molecular transistor, this energy cost can be tuned to zero by applying a voltage to the gate electrode. At a particular gate voltage, the electrostatic potential is such that an extra electron can hop from the source onto the molecule. However, Coulomb repulsion forbids a second, extra, electron hopping on at the same time — the first electron must leave the molecule, moving into the drain, to make way for the next electron. This one-by-one electron motion, governed by the quantum of electron charge, is known as single-electron tunnelling.

But there is another quantum property important for electron transport through small objects — the electron spin. Electrons each carry one half-unit of spin in one of two configurations, defined as 'up' or 'down'. As there is no preference for the direction of the spin, the lowest-energy (ground) state of the system is a combination of up and down spins. To reach this ground state, an electron spin must flip between up and down, and this can be arranged by replacing an up-spin electron on the molecule by a down-spin electron from one of the electrodes. This spin-flipping, driven by the desire of the system to be in its ground state, enforces an exchange of electrons between molecule and electrodes through a process called the Kondo effect[8].

In the experiments by Park *et al.*[3] and Liang *et al.*[4], the molecule is tuned between two states that differ by one charge and one spin unit. In one state, the conduction mechanism is single-electron tunnelling. In the next state, with an odd number of electrons on the molecule, electron transport is mediated by the Kondo effect. Remarkably, when the Kondo effect dominates, the conductance reaches values close to the quantum limit (which is $2e^2/h$, where e is the electron charge and h is Planck's constant) for a perfectly conducting one-dimensional wire. This result is quite remarkable, considering the intrinsic difficulty of establishing good electrical connection between a molecule and a metal electrode.

Do these realizations of a single-atom transistor mean that molecular electronics is just around the corner? That goal may be a little closer, but there is still a long road ahead before atomic or molecular transistors can be assembled into viable, dense, fast logic-circuits. Right now, these single-molecule or single-atom transistors are no competition for silicon transistors. But they will serve both scientifically, for studying electron motion through nanoscale objects, and technologically, for developing chemical techniques with which to fabricate electronic devices on single molecules. ■

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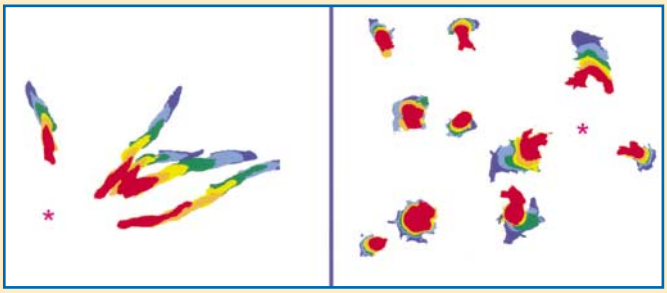
Cell motility

The attraction of lipids

The pictures reproduced here aren't just pretty — they reveal something fundamental about how cells move towards the source of an attractant chemical. The left image shows the behaviour of normal cells of *Dictyostelium discoideum*, a type of slime mould. The cells on the right lack an enzyme called PTEN. The colour scale, from blue to red, indicates how each cell moves over time. The normal cells are clearly moving towards a chemical source (asterisk), but the mutant cells seem less sure where they're going.

The images are taken from a paper by Miho Iijima and Peter Devreotes (*Cell* **109,** 599–610; 2002). Together with work by Satoru Funamoto *et al*. (*Cell* **109,** 611–623; 2002), this study reveals the importance to motility of enzymes — including PTEN — that alter the lipid content of cell membranes.

Many cells need to move up a concentration gradient of a given chemical ('chemoattractant'); in humans, for instance, immune cells migrate towards signals emitted by invading microorganisms. Cells must sense the gradient and then extend protrusions ('pseudopodia') in the direction of movement. Filaments of the protein actin form the skeleton of pseudopodia.



Studies with lipid-binding proteins suggested that the lipid content of cell membranes forms a gradient during chemoattraction, with 3-phosphoinositides being concentrated at the front edge. These are thought to bind signalling proteins, leading to the changes needed for movement. But how does the lipid imbalance come about? This question is tackled in the new papers.

Funamoto *et al.* started by studying phosphatidylinositol-3-OH kinases (PI(3)Ks), enzymes that produce 3-phosphoinositides, in *D. discoideum*. When cells were placed in a chemoattractant gradient, two different PI(3)Ks moved to the membrane at the leading edge, with similar kinetics to 3-phosphoinositide-binding proteins. Membrane-bound PI(3)Ks seemed to trigger the formation of pseudopodia.

So the localization of PI(3)Ks could explain the generation of 3-phosphoinositides at the leading edge. But the concentration of these lipids tails off sharply towards the rear of a cell, hinting that an enzyme that degrades them might be at work there. Both groups investigated a possible candidate — PTEN. When Funamoto *et al.* overexpressed this enzyme in *D. discoideum*, the cells moved more slowly and became less polarized in response to a chemoattractant. Iijima and Devreotes engineered *D. discoideum* lacking PTEN, and again the cells moved abnormally, taking a circuitous route to the chemoattractant. The cells also produced pseudopodia more erratically, sometimes at the back, and had more actin filaments than normal. Finally, both groups found that PTEN is usually located at the rear of moving cells.

This suggests that PTEN and PI(3)Ks help to produce a gradient of 3-phosphoinositides, which is much steeper than the chemoattractant gradient. The lipid gradient translates into the correct localization of key signalling proteins and actin filaments, and so into directed movement. But how these enzymes are moved about the cell, and how they interact with other chemoattractant-sensing pathways, remains to be seen. **Amanda Tromans**