Most (80%) of the *BRAF* mutations detected by Davies *et al.* resulted in a single amino-acid change in the region of the enzyme that catalyses phosphorylation. This alteration involved the replacement of a neutral amino acid (valine at position 599) by a negatively charged one (usually glutamic acid). The mutation probably leads to constitutive activation of the MAPK pathway, by mimicking the transient phosphorylation of threonine 598 and serine 601 that occurs during normal signalling[5]. With this growth switch stuck in the 'on' position, tumour development is favoured.

Davies *et al.* found this mutation in several cancer types, mainly those known to have *RAS* mutations. For most cancers the rate of *BRAF* mutation was modest, occurring in fewer than 20% of the cell lines studied. But in melanoma cell lines, the authors found *BRAF* mutations at the staggering rate of 59%. Davies *et al.* strengthened these data by finding *BRAF* mutations in 80% of short-term melanoma cell cultures and 66% of uncultured melanomas, strongly suggesting that the high mutation frequency in cell lines was not an artefact of cell culture. This represents a clear step forward in understanding the biology of melanoma, which has so far yielded few of its genetic secrets.

Melanoma is an aggressive skin cancer that is derived from pigment cells (melanocytes). The disease can be cured surgically if caught early, but once melanoma cells have spread to other parts of the body they are resistant to most current treatments. Until now, *CDKN2A* — which encodes p16, an inhibitor of the cell-division cycle — was the most commonly mutated gene in melanoma, being inactivated by a variety of mechanisms in some 25% of sporadic melanomas[6]. Less frequent molecular alterations have been reported in *NRAS*, a member of the *RAS* family, and the tumour-suppressor gene *PTEN*.

BRAF is part of key melanocyte-specific MAPK pathways, such as that involving melanocyte-stimulating hormone, which activates the melanocortin-1 receptor on the cell surface. This may account for the high frequency of *BRAF* mutations in melanomas relative to other cancers[7]. Could *BRAF* be a breakthrough target for future treatments for melanoma? This could be so, and the intense attention that will now be directed at this gene will certainly lead to important insights. However, the identification of *RAS* mutations 20 years ago has not yet led to clinically useful *RAS*-targeted therapies.

The discovery of *BRAF* mutations[1] is a convincing validation of the Cancer Genome Project's high-throughput strategy. The mutations might not have been discovered for years without this type of approach. Now the project's investigators face the challenge of going through the rest of the genomic haystack. For their success to continue, they must be certain that their screen is sensitive, thorough and efficient.

Challenges remain; for instance, the process of locating all genes in the human genome (annotation) still continues. Indeed, the precise number of genes is still a matter for debate, somewhat obscuring the goal of testing them all. Also, this approach depends on having DNA from cultured tumour cells; that may be difficult to achieve for some important tumours, such as prostate and pancreatic cancer, which are not easy to culture.

So where does this gargantuan effort leave the many researchers studying the genetics of cancer progression? Although it is too soon to declare focused, smaller-scale research obsolete, the Cancer Genome Project — as yet unrivalled — is likely to produce a steady flow of discoveries. Nonetheless, the identification of a cancer-specific mutation is but the first step in a lengthy process. Further studies are needed to determine when *BRAF* mutations occur during tumour evolution, what their biochemical effects are, and the possible implications for treating cancer. ■

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Materials science

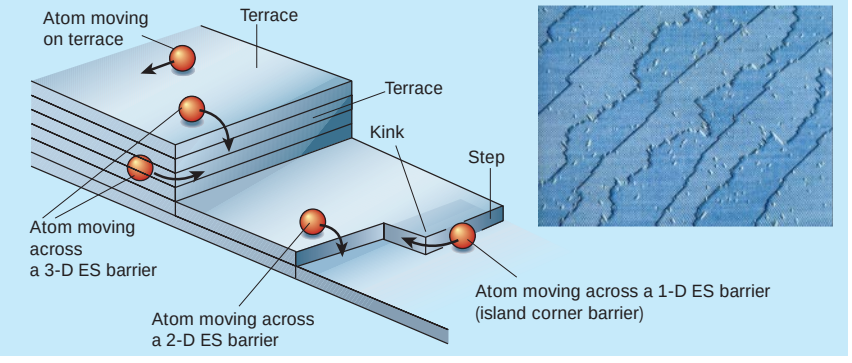
Thin-film cliffhanger

Max G. Lagally and Zhenyu Zhang

Thin films are grown ideally one atomic layer at a time, but atoms can move along and between layers. The model for film growth has now been extended to describe how atoms tumble over 'cliffs' between layers.

Many modern technologies depend on our ability to grow thin films. In highly refined semiconductor technologies (such as solid-state lasers in compact-disc players or fast electronic components in mobile phones), films must be nearly perfect, grown seemingly one atom at a time, and individual layers of a composite film may be only a few atomic layers thick. In less critical technologies, films are deposited with essentially the same methods but with less need for perfection — protective coatings, decorative coatings, wear coatings and so on. Even something as simple as a potato-chip bag may have a thin-film coating that acts as a moisture barrier.

We think of film growth in terms of atoms or molecules 'raining' down on a surface, and then finding the proper sites to come to rest and form a layer. But in crystal growth in



BRIAN SWARTZENTRUBER

Figure 1 **The terrace-step-kink (TSK) model of a thin-film surface. The surface consists of terraces separated by steps; a kink is a step on a step. Atoms travelling over steps that are one-atomic-layer high must cross an energetic barrier, the two-dimensional Ehrlich–Schwoebel (ES) barrier. At kinks, atoms experience the 'corner-crossing' barrier, a one-dimensional version of the ES barrier. Liu *et al.*[1] have identified a three-dimensional ES barrier for atoms travelling over steps that are four or more atomic layers high, or over the edges between two facets. The validity of the TSK model for thin films has been confirmed by the detailed imaging made possible by the scanning tunnelling microscope. The inset image shows the surface of a thin film of silicon (100 nm × 80 nm). Terraces separated by single-atom-high steps with many kinks can be seen, stepping down across the image from upper left to lower right. The white spots are atomic vacancies in the terraces.**

general — whether it be the formation of gems over geological timescales, the appearance of salt crystals on your skin after a dip in the ocean, or the growth of alum crystals in a school science experiment — the atomic processes that occur always follow the same rules. Writing in *Applied Physics Letters*, Liu *et al.*[1] have now put in place the final piece in our understanding of the rules that govern how atoms move from one layer to another as films or crystals grow.

Consider a marble rolling off a table. It rolls over the edge, never pausing to 'think' that it might fall and break. Yet if we walk up to the edge of a cliff, we instinctively slow down, perhaps peer carefully over the edge, and draw back. There is a 'barrier' that keeps us from going forward. What would an atom do in the analogous situation?

The terrace-step-kink (TSK) model[2], developed by Burton, Cabrera and Frank in the early 1950s, elegantly describes the atomic-scale morphology of the surface of a crystal (Fig. 1). When an atom lands on the surface, it diffuses along the 'terrace' formed by that film layer, trying to find the best place (from the point of view of its free energy) to settle — frequently a lower terrace. But an atom coming to the edge of a terrace behaves like a human on a cliff: it feels a barrier that prevents it going over the edge.

In 1966, Gert Ehrlich performed elegant experiments[3] using field–ion microscopy in which he put a single atom on an atomic terrace and observed its motion. He saw that atoms were preferentially reflected back at the edges of a terrace. He explained this behaviour in the following way. The atom on a terrace has a certain number of nearest neighbours (its coordination number) and the bonding to these neighbours provides stability for that atom. As it reaches the edge of a terrace, it suddenly has fewer neighbours, and the resulting decrease in the binding energy is manifested as a barrier for diffusion over the edge. Richard Schwoebel independently proposed[4] a similar model at the same time.

But for more than 20 years this idea languished — until the advent of the scanning tunnelling microscope made it possible to observe the atomic-scale morphology of surfaces over mesoscopic regions, and provided vivid visual confirmation of the TSK model (Fig. 1). Because film-growth studies at the atomic level were now possible, the effects of barriers to atom transport between terraces in a growing crystal or film could be directly observed.

A reflective wall at the edge of a terrace, which became known as the Ehrlich–Schwoebel (ES) barrier, hinders the descent of atoms to lower levels. This increases the chance of nucleation and growth of a new film layer on top of the terrace when more atoms arrive from the deposition source. In 1991, Villain showed[5] that an ES barrier (which is a two-dimensional phenomenon) creates an effective 'uphill' gradient, leading to unstable growth and the creation of roughness in the film — an undesirable feature. Thus the two-dimensional ES barrier dictates the three-dimensional morphological evolution of growing films.

But the concept of the ES barrier also extends to other dimensions. As the figure shows, a step separates one terrace from another; a kink is the one-dimensional analogue: a 'step on a step'. We have pointed out[6,7] that there should also be a one-dimensional analogue to the phenomenon Villain described — that an atom moving along a step edge should feel a barrier preventing it crossing this kink because of its reduced coordination number. The ultimate kinks occur at the corners of a two-dimensional crystal (an 'island'), where two step edges meet. An atom diffusing along one edge feels a barrier to crossing to the adjacent edge: this 'corner-crossing barrier' can cause two-dimensional islands (one-atomic-layer high) to develop rough, or even fractal, shapes. This corner-crossing barrier — in fact, a one-dimensional ES barrier — can also induce growth instability in the morphology of a three-dimensional film[8,9]. Indeed, films may actually grow more smoothly if this barrier is large.

If a number of identical terraces were stacked on top of each other, the simple corner becomes a line or a ridge between two crystal facets. Following on from their earlier work[10], Liu *et al.*[1] propose that there is also a three-dimensional ES barrier that influences atom transport from one facet across this edge to the adjacent facet. The authors point out that the magnitude of the three-dimensional ES barrier may be quite different from that of the two-dimensional ES barrier; the latter may, in fact, be zero but the three-dimensional barrier can be quite high.

Liu *et al.* also show that, for transitions over a step edge between adjacent terraces, the two-dimensional barrier becomes a three-dimensional barrier as the height difference between the two terraces increases (Fig. 1). For the specific example of aluminium, the transition from two-dimensional to three-dimensional ES barrier is complete if that height is four atomic layers or more[1,10].

So the picture is complete: the growth morphology and shape of every crystal — whether it is two-dimensional (a single-atomic-layer-high island), 'two-and-a-half-dimensional' (a nearly flat film with some roughness) or three-dimensional (a small nanocrystal) — is controlled by the magnitude of barriers felt by atoms as they approach a 'cliff' and decide whether they really do want to step off the edge. A proper accounting for these barriers in film growth will determine the ultimate quality, reliability and stability of films grown for a great variety of purposes. ■

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100 YEARS AGO

Mr. Marconi's Results in Day and Night Wireless Telegraphy. **Reading a brief account of these results in the *Times* of June 14, I perceive that Signor Marconi advances in explanation of the greater distance at which night signals were received, that the day signalling is affected by diselectrification of the transmitting elevated conductor. If — as I gather — Signor Marconi is referring to his observations made at positions in the Atlantic, west of England, the waves travelling westwards, may not æther drift in the earth's orbital path be concerned in producing the effects observed? The waves advancing against the orbital æther stream in the daytime, with it at night, might be supposed to give rise to conditions analogous to those which affect the transmissibility of sound against or with a high wind. It will assist if we assume a retarded æther drift near the earth's surface and free motion above. But still, the difficulty in the explanation resides in the very great magnitude of the effects observed. I write merely by way of suggestion, and in very considerable ignorance of almost every particular involved in this explanation.** **J. Joly**

From *Nature* 26 June 1902.

50 YEARS AGO

In the last section of a recent paper, Dirac discusses his formulæ with the following words: "An important feature of the new theory is that it involves only the ratio *e*/*m*, not *e* and *m* separately. This is what one should expect in a purely classical theory. The existence of *e* should be looked upon as a quantum effect, and it should appear in a theory only after quantization, and not be a property of classical electrons". If this point of view be accepted, some properties of electrons which have always been regarded as classical should be regarded as quantum effects; for example, the scattering of long electromagnetic radiation by free electrons. … I am further convinced that it is futile to deal with the electron and its electromagnetic field separately, but that the fields of all mesons together with the electromagnetic field should be simultaneously considered. I have indicated a way of doing this elsewhere, and though I am far from thinking that this suggestion is right, I am still convinced that the solution must be sought in this direction. **Max Born**

From *Nature* 28 June 1952.

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Plant–microbe interactions

A receptor in symbiotic dialogue

Herman P. Spaink

Proteins that help plants connect with symbiotic microbes have been identified. These proteins are related to receptors in animals and plants that function in the innate immune system and organ development.

Many plants can grow on soils that are poor in nutrients, and they do so by forming symbiotic associations with microbes. These associations require a molecular dialogue between the two partners. On pages 959 and 962 of this issue, Stracke *et al.*[1] and Endre *et al.*[2] describe how they have identified genes that encode a plant protein that is essential to the dialogue.

Important examples of microbes involved in symbiosis are bacteria called rhizobia and fungi — 'arbuscular mycorrhizal fungi' — that respectively supply the plant host with nitrogen- and phosphorus-containing nutrients[3,4]. In return, the microbes receive carbohydrate nutrients from the plant. The genes identified by Stracke *et al.* and Endre *et al.* seem to belong to a large family of plant and animal genes that encode a particular class of receptor proteins. These proteins are characterized by having a repeated motif rich in the amino acid leucine — called a leucine-rich-repeat (LRR) — in an extracellular domain[5–7]. In animals the proteins comprise a group, known as the Toll-like receptors, that function in the innate immune system[8]. In plants they belong to a subfamily that has in common an intracellular serine/threonine kinase domain that triggers a signalling cascade inside the cell. Several members of this plant subfamily are involved in defence against pathogenic microbes, or in shoot development[9] (Fig. 1).

It is not too surprising that receptors involved in plant–microbe symbiosis belong to the LRR receptor subfamily, given that it is one of the largest groups of receptors in the plant kingdom with, for instance, 174 members in the 'model' plant *Arabidopsis* alone[10]. But it is surprising that Stracke *et al.* and Endre *et al.* found a function for a highly similar LRR receptor in different plant species — not only in the model legumes *Lotus japonicus*, *Medicago sativa* and *Medicago truncatula*, but also in the agriculturally important crop plant, pea (*Pisum sativum*). In all, the two groups carried out a genetic analysis of nine mutants that have defects in the early stages of symbiosis, discovering the involvement of a member of the LRR receptor family and by implication its key role in symbiosis.

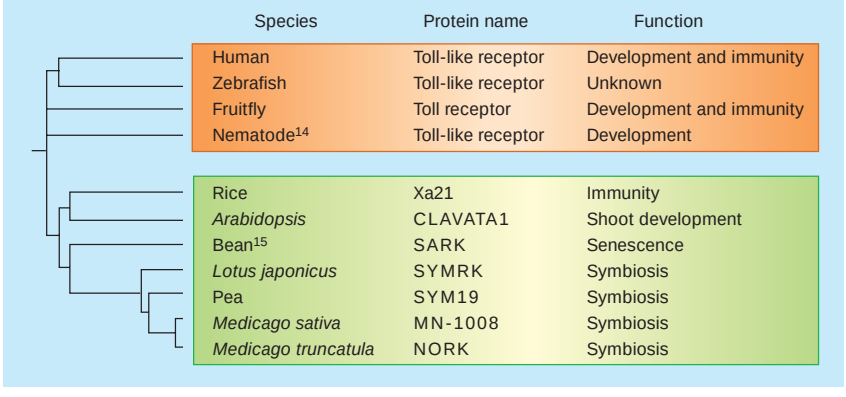

Figure 1 **Comparison of members of the protein family of receptors containing extracellular leucine-rich-repeats (LRR). This tree of protein relatedness compares examples from various subfamilies in animals and plants, and indicates the breadth of species in which the receptors are found, and the variety of functions that they have. The receptors' involvement in plant–microbe interactions, as a component of the plant side of the molecular dialogue in symbiosis, is described by Stracke *et al.*[1] and Endre *et al.*[2] in this issue. The plants concerned are the model legumes *Lotus japonicus*, *Medicago sativa* and *Medicago truncatula*, and the pea (*Pisum sativum*). The examples not referenced above are reviewed in refs 6 and 8. For zebrafish, the assignment is based on data (BG304206) submitted to Genbank by S. Johnson. CLAVATA1 is the receptor that recognizes CLAVATA3.**

For the rhizobium–plant interaction, various signal molecules produced by the microbial partner have been identified. One group — the Nod factors — has attracted much attention because Nod factors specifically trigger the host plants (belonging exclusively to the legume family) to produce a specialized microbe-accommodating organ, the root nodule[3]. But little is known of the plant factors that recognize rhizobial signal molecules. And even less is known of plant interactions with arbuscular mycorrhiza: for this microbe, no signal molecules have been identified.

In finding a receptor protein involved in recognizing signal molecules from both rhizobia bacteria and arbuscular mycorrhiza, Stracke *et al.*[1] and Endre *et al.*[2] have provided a long-awaited breakthrough. Identifying the genetic basis of microbial recognition in the plant hosts has been hampered by technical difficulties, which are especially acute for plants that form strong symbiotic relationships. As exemplified by legumes, such plants have relatively large genomes, which in some cases exceed the size of the human genome. That makes identification of point mutations — single-nucleotide changes in DNA — extremely difficult. Furthermore, in plants, gene-knockout techniques are still in their infancy[11,12]. Stracke *et al.* and Endre *et al.* circumvented these difficulties by making optimal use of the advantages offered by classical plant genetics in legumes — the production of large numbers of mutants and genome-map-based cloning — and the increased availability of nucleotide sequence data.

The results open the way for detailed analysis of the direct binding partners, and downstream signalling pathways, that are associated with microbial recognition. Such analysis may soon provide further insight into the similarities with signal pathways involving other classes of LRR receptor, and could reveal connections with the recognition mechanism of factors produced by pathogenic microbes or signalling peptides involved in development.

The future bottleneck in studying this receptor family is our lack of knowledge about the signal molecules that are recognized by the receptors. Up to now, a triggering factor has been identified for only two plant LRR receptor proteins. These factors (microbial flagellin[5] and the plant differentiation factor called CLAVATA3) are extracellular proteins. The structural evidence is consistent with the idea that LRR sequence