C_{60}^{2+} ions, focused to a spot size of a few micrometres. The yields of secondary ions obtained using the C_{60} source are typically 50 to 200 times higher than from using gallium LMIGs. The gold-cluster LMIG can produce Au , Au_2^+ and Au_3^+ ions. Secondary-ion yields produced using Au_3^+ ions are typically 10 to 100 times higher than for Ga^+ ions. As the ions from this source can be focused down to smaller spot sizes than with the C_{60} source, it will be the preferred ion source for imaging experiments. On the other hand, the C_{60} source produces a higher yield of molecular fragments from organic and biological samples than the gold source, so it will be preferred for spectroscopic experiments.

Using gallium and indium LMIGs, the spatial resolution for imaging with low-ion-yield molecular fragments is typically limited to a few micrometres: decreasing the pixel size below one micrometre typically causes the number of secondary ions per pixel to drop to essentially zero. But with the increased yield of the gold-cluster LMIG, sub-micrometre spatial resolution could be attainable for molecular SIMS imaging. This will significantly improve the capability of SIMS for imaging the spatial distribution of drugs, proteins and oligonucleotides in a wide range of biomedical devices and sensors.

Although these new cluster-ion sources offer exciting possibilities for SIMS analysis (such as molecular-depth profiling capabilities for organic samples¹¹, something most SIMS analysts had assumed was impossible), several areas still require additional study. At present it is not understood how cluster-ion beam sputtering can simultaneously achieve higher secondary-ion yields and lower damage rates. Several explanations have been proposed: for instance, perhaps it is because the total ion energy is distributed over all the atoms in the cluster, or because there is overlap in the energy cascades produced when the polyatomic ion strikes the surface. Other

questions, such as whether 'increased yield with decreased damage' holds for all types of sample, and whether the concentration of surface species could be quantified, are also unanswered. Further experimental and theoretical research is needed to address these and other issues.

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Medicine

Smoke signals for lung disease

Anita B. Roberts

A group of proteins that might confer susceptibility to emphysema has been identified. One of them is transforming growth factor- β , and the discovery highlights the many ways of activating this protein in health and disease.

Emphysema is a lung disease that is predicted¹ to become one of the top five causes of death and disability worldwide by 2020. Cigarette smoking is the greatest risk factor for this disease. Despite this correlation, however, only about 15–20% of cigarette smokers develop emphysema. The fact that these susceptible individuals are generally clustered into families hints that there may be certain genes that predispose people to smoking-induced emphysema. On page 169 of this issue, Morris and co-workers² describe how they used clues from gene-array technology and manipulation of the mouse genome to implicate an entirely new group of possible susceptibility genes.

Unlike asthma, in which the flow of air through the lungs is temporarily obstructed,

emphysema is characterized by a progressive airflow restriction that results from permanent enlargement of the lungs' peripheral air spaces and loss of lung elasticity. In smoking-related emphysema these changes are often attributed to the destruction of lung connective tissue through enzymatic degradation of elastin, the main component of the elastic fibres of lung tissue¹.

Matrix metalloproteinases (MMPs) are zinc-dependent enzymes that can degrade connective tissues, including elastic fibres^{1,3}. The gene for the MMP12 protein in particular has been considered a strong candidate for conferring susceptibility to emphysema. MMP12 is produced by macrophages — inflammatory cells that infiltrate smokers' lungs — and destroys not only elastin itself,

Solar System

Close encounter of the cometary kind

Last month, the Solar and Heliospheric Observatory, run jointly by the European Space Agency and NASA, enjoyed a spectacular view, as the comet C/2002 V1 (NEAT) approached the Sun at a distance of around 15 million kilometres — roughly one-tenth of the distance from the Sun to the Earth. The comet is seen here over a 69-hour period.

Hourly images were fed back by the large-angle and spectrometric coronagraph, an instrument studying the Sun's corona, or gas halo. To

detect the corona, the coronagraph blots out the disk of the Sun (the star's position is indicated by white circles).

As the comet orbits the Sun, its bright ion tail is deflected by the magnetic field of the solar wind. The

striking feature in the centre picture is a huge eruption of gas from the corona.

Alison Wright

Figure 1 Effects of activating and inhibiting transforming growth factor- β (TGF- β) in the lungs. **a**, The $\alpha 5 \beta 6$ integrin protein is found on epithelial cells, such as those that line the lungs. When the latency-associated peptide (LAP) binds to $\alpha 5 \beta 6$ integrin, it enables TGF- β to bind to its receptor on macrophages⁵ (and fibroblasts; not shown). This results in reduced synthesis by macrophages of the matrix-degrading enzyme MMP12 and of inducible nitric oxide synthase (iNOS). It also results in enhanced production by fibroblasts of components of the extracellular matrix (ECM) and of proteins, such as TIMP-1, that inhibit matrix-degrading enzymes. **b**, In mice lacking $\beta 6$ integrin, the prevention of TGF- β binding to its receptor results in reduced production of ECM and enzyme inhibitors and increased production of MMPs and iNOS. This protects against pulmonary fibrosis⁵, but, as Morris *et al.* show², the resulting matrix-degrading environment leads to destruction of lung tissue and emphysema.

but also an inhibitor of another type of elastin-degrading enzyme. Moreover, levels of MMP12 are higher than normal in the lungs of mice exposed to cigarette smoke, and deletion of the MMP12 gene protects mice from developing emphysema caused by prolonged exposure to cigarette smoke³. In addition, variations between people in the sequence of their MMP1 and MMP12 genes have been linked to a predisposition to smoking-related emphysema⁴.

Morris *et al.*² have now used genetic manipulation in mice to reveal a new mechanism that leads to abnormal production of MMP12 and to late-onset emphysema that closely mimics the human disease. These authors had previously studied integrin $\alpha 5 \beta 6$, a protein found on the cell surface. It consists of two subunits, $\alpha 5$ and $\beta 6$, and its job is to sense components of the extracellular matrix around cells. The authors found that deleting the $\beta 6$ subunit, which occurs only in epithelial cells (such as those that line the lungs), protects against pulmonary fibrosis (scarring)⁵.

How does this work? It is possibly no accident that the so-called latency-associated peptides of the transforming growth factor (TGF) $\beta 1$ and $\beta 3$ proteins carry a motif that can recognize $\alpha 5 \beta 6$ integrin, just as matrix components do. When these peptides bind to $\alpha 5 \beta 6$ integrin in the lungs, they activate extracellular latent TGF- β , which can then bind to receptors on nearby cells, such as macrophages or fibroblasts, and activate signalling^{5,6} (Fig. 1a). This increases the production of matrix proteins by fibroblasts and reduces the production of matrix-degrading metalloproteinases by macro-

phages, leading to abnormal accumulation of matrix components and scarring. So, when $\beta 6$ integrin is deleted, this mechanism for activating latent TGF- β no longer works: matrix metalloproteinases are still generated, matrix production is reduced, and scarring is prevented⁵ (Fig. 1b). Although it has long been recognized that TGF- β can enhance the accumulation of extracellular matrix and promote fibrosis in many tissues, these studies were the first to emphasize the importance of its activation from latent forms in disease.

Morris *et al.* now show that ageing mice lacking $\beta 6$ integrin also develop emphysema. Their disease is characterized by enlargement of the air spaces, infiltration of the lungs by activated macrophages and — as shown by array technology — a 100-fold increase in the amount of MMP12 messenger RNA in the lungs (a measure of how strongly the MMP12 gene is expressed there). MMP12 is clearly necessary for disease onset in this case, because mice lacking both this protein and $\beta 6$ integrin do not develop emphysema.

As TGF- β strongly suppresses MMP12 expression in macrophages⁷, it again seemed likely that mice lacking $\beta 6$ integrin express MMP12 — and develop emphysema — because latent TGF- β in the lungs is not activated (Fig. 1b). This idea is supported by Morris and colleagues' finding that overproduction of either normal $\beta 6$ integrin, or mutant forms of it that can still activate latent TGF- β , decreases MMP12 expression in the lungs of ageing $\beta 6$ -deficient mice, and blocks the development of emphysema. The use of a mutant $\beta 6$ integrin that cannot bind

or activate latent TGF- β does not have these effects. To show more directly that a failure to activate latent TGF- β underlies emphysema in this model, the authors also generated $\beta 6$ -deficient mice that produce permanently active TGF- β . The early signs of emphysema did not develop.

These exciting results broaden the spectrum of factors involved in emphysema to those that activate latent TGF- β in the lung and, by inference, to TGF- β -triggered signalling molecules such as its receptors and intracellular proteins known as Smads⁸. Smad3, for instance, is known to be required for TGF- β to inhibit macrophage activation, and to suppress the production of MMP12 (refs 7, 9). TGF- β also reduces the expression of an enzyme called nitric oxide synthase^{7,9}, presumably leading to decreased levels of reactive nitrogen species — molecules that can amplify inflammation and so contribute to diseases such as emphysema. By contrast, TGF- β activates production of TIMP-1, an enzyme that inhibits matrix metalloproteinases. So, a combination of factors may contribute to the emphysema seen in $\beta 6$ -integrin-deficient mice: an increase in the amount of MMP12 and nitric oxide synthase, and a decrease in TIMP-1 levels.

TGF- β is also involved in suppressing tumour development, and this invites comparisons between the effects of reduced TGF- β signalling in emphysema and lung cancer⁸. Last year, a defect in latent TGF- β -binding protein-4 — a structural component of the extracellular matrix that also affects the targeting of latent TGF- β to the matrix — was shown to result in colon cancer¹⁰. This was again associated with a drastic reduction in TGF- β levels and signalling. Together, these studies draw attention to the often overlooked role of the many tissue-specific, and possibly disease-specific, mechanisms for activating latent TGF- β , which are important not only in disease but also in maintaining normal tissue integrity. Perhaps more importantly, the work of Morris *et al.* provides new potential targets for investigations of candidate susceptibility genes and for the development of drugs to treat or prevent emphysema. ■

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