NEWS & VIEWS

NANOTECHNOLOGY

Patterns from molecular corrals

Michael Grunze

Many nanotechnology devices will require components that consist of arrays of molecules positioned on surfaces with nanometre precision. One way to make these is to let the molecules organize themselves.

A major challenge in nanotechnology is to find a way of positioning molecules and atoms on surfaces in regular patterns, with nanometre precision yet over large surface areas. Reporting on page 618 of this issue, Madueno *et al.*[1] describe just such a method. They have corralled self-assembling films within the pores of a two-dimensional network of molecules on a substrate, thereby forming patches of film in a repeating pattern that extends over a wide area. Each patch consists of spatially localized molecules that have chemical groups that perform a specific function. Crucially, the resulting system is robust enough to be used for technological applications, such as in nano-sized components for sensor devices.

Currently, one of the best methods for creating patterned surfaces is optical lithography. In this process, a substrate is coated with a light-sensitive chemical (a photoresist), so that a design can be created by exposing the photoresist to ultraviolet light. The resulting pattern is used as a template for physical or chemical modification of the substrate. The design on the substrate is created by shining ultraviolet light through a 'mask', and herein lies the problem. The accuracy of the lithographic process is limited both by the wavelength of the light (which is usually relatively long — hundreds of nanometres) and the precision with which masks can be manufactured. The problem is partly alleviated by projecting the image from the mask through a system of lenses, to reduce the size of the image that reaches the photoresist. In this way, surfaces can be etched with designs at scales below 100 nanometres. But this still isn't small enough for proposed nanotechnology applications. Nevertheless, optical lithography is tremendously successful, and is used by the semiconductor industry to make microchips for computers.

For smaller surface features, only 'serial' methods are available, in which each part of the pattern is created one after the other, rather like drawing a design with a pen. These techniques include electron beam lithography (in which a pattern is formed in a resist using electron beams), or depositing molecules on a surface using the tip of an atomic force microscope (AFM). Patterns can be made with nanometre resolution with these techniques, but they are impractical for applications involving large surface areas — although arrays of thousands of AFM tips have been used to deposit compounds across wider areas, in a process known as dip-pen lithography.

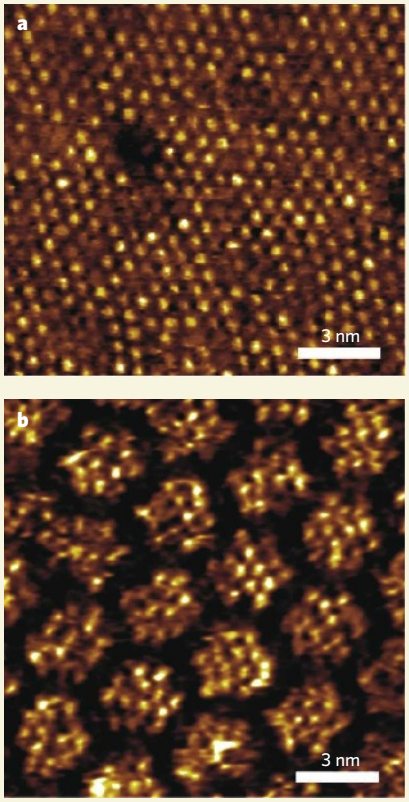

Figure 1 | Patterned arrays of molecules. a, Thiol molecules self-assemble on gold surfaces to form monolayers of molecules. In this image, taken with a scanning tunnelling microscope, each dot represents a single thiol molecule (adamantanethiol). **b**, Madueno *et al.*[1] allowed a two-dimensional, porous network to self-assemble from two different kinds of aromatic molecules on a gold surface. On treatment of the network with adamantanethiol, monolayers form on the gold surface within the pores, yielding a regular pattern of hexagonal monolayers. Dark regions show the 'frame' of the molecular network. (Images courtesy M. Buck.)

But there is another strategy. The smallest unit of a chemical pattern is an individual molecule, and appropriately designed molecules can self-assemble into molecular films with a regular order. An ideal approach would therefore be to use an ordered, self-assembled network as a template to arrange other molecules with nanometre-scale precision.

Compared with the self-assembly of macromolecular complexes in solution, the analogous process on a surface is less well developed[2,3]. Assemblies of molecules that form open network structures are of particular interest as surface templates because they contain cavities that can be filled by 'guest' molecules. A wide variety of molecules can in principle be accommodated, so that the overall properties of the networks could be modified simply by changing the guests. So far, only a few model systems have been studied, and in these systems the guests are simple molecules that aren't useful for any applications and don't greatly affect the properties of the network[4–6]. In any case, these model systems are too fragile to be used for nanotechnology applications.

Madueno *et al.*[1] now describe a robust, stable network of molecules that survives the formation of films (known as self-assembling monolayers, or SAMs) in its molecular corrals (Fig. 1). This provides a simple method for generating patterned SAMs of molecules that could, for example, bind specific biomolecules in a diagnostic application, or be used as a template for metal deposition. Furthermore, the authors show for the first time that such a network can be strong enough to survive further modification in solution. They also demonstrate that their network–SAM hybrid is stable in electrochemical experiments, which suggests that such structures could be processed to produce arrays of nanometre-sized structures made from metals or semiconductors.

But the implications of the work extend beyond practical applications — fundamental scientific questions could also be addressed using Madueno and colleagues' approach. If objects (molecules, atomic clusters or nanoparticles) can be attached to SAMs that are corralled in a network, this would allow the effects of confinement, at scales relevant to

quantum processes, to be studied. For example, how does such confinement affect SAM formation, and what is the smallest size at which they can form? The answers to these questions will be useful for determining how small certain nanotechnology devices could be.

One could also imagine narrowing down the size of the pores in a network until only a single object can be accommodated in each pore. The intermolecular distance between guest objects would then be controlled by the structure of the network. Such a system would be useful for studying the unfolding of polymers and proteins; energy transfers between molecules or nanoparticles; or confinement effects in chemical or enzymatic reactions. Another possibility would be to use the network–SAM hybrid as a template for three-dimensional self-assembled structures.

It remains to be seen how flexible self-assembling network–SAM structures will be. Madueno *et al.*[1] used gold substrates in their experiments, as this is the metal of choice for SAM formation. Alternative substrate materials have yet to be tried, but it is safe to assume that other metals will work. Many different SAM molecules are also available, each with different chemical groups attached. It is currently unclear whether all of these SAM molecules will be suitable as guests, however, as some of the appended groups might react with host molecules at random positions in the network, destroying the order of the resulting system. Finally, the molecules that form the network should also be investigated — to what extent can they be modified, or varied in size?

Madueno *et al.* have provided a basic recipe for patterning surfaces that allows the promising possibilities of precisely delineated arrays of molecules to be explored. No doubt others will come up with their own variations with which to explore the limits of two-dimensional host–guest arrays, to eliminate imperfections and, perhaps most excitingly, to develop applications for them. ■

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CANCER

Ins and outs of tumour control

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When a potentially dangerous cell can't be repaired, it must be either stopped or killed. Premature senescence of cancerous cells is one such 'stop' mechanism, in which immune mediators play an unexpected part.

Various mutations can make normal mammalian cells cancerous. Luckily, several built-in mechanisms that inhibit tumour formation are in place. For example, a host of molecular factors, including tumour-suppressor proteins, blunt the accumulation of potentially dangerous cells by promoting either cellular senescence or apoptosis (programmed cell death)[1]. But tumour suppressors are neither infallible nor work in isolation. So the quest is on for other natural anticancer agents. In papers published in *Cell*, Kuilman *et al.*[2] and Acosta *et al.*[3] describe the role of several secreted immune mediators in promoting cellular senescence in response to oncogene activation.

Senescent cells are metabolically active and can secrete various proteins, including growth factors, matrix metalloproteinases, protease inhibitors and cytokines, each of which can have multiple effects on the tumour microenvironment and, ultimately, on tumour development[4,5]. The two teams[2,3] also independently arrive at the secretome (a collection of secretory cellular molecules) as a central switch in oncogene-induced cellular senescence.

Kuilman *et al.* wanted to identify genes that respond differentially to the $BRAF^{V600E}$ oncogene, and came upon a footprint of immune mediators (cytokines and chemokines) that are induced only in senescent cells. For example, they find that, in fibroblasts expressing $BRAF^{V600E}$, signals from this oncogene induce secretion of the cytokine IL-6, which is essential — although insufficient — for the induction and maintenance of senescence in the very cells that secrete them (Fig. 1).

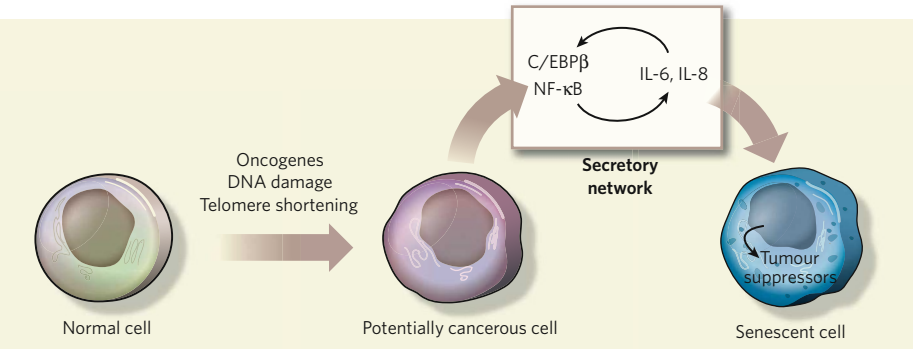

Figure 1 | Intracellular and secreted proteins control tumour development. Oncogenic signals, DNA damage and telomere shortening can all turn normal cells into potentially cancerous ones. Two groups[2,3] find that such affected cells induce a secretory network (IL-6, IL-8, C/EBPβ and NF-κB), which in turn triggers expression of tumour-suppressor proteins, such as $p15^{INK4b}$, $p16^{INK4a}$ and p53, and premature senescence to prevent tumorigenesis.

The authors also find that the gene transcription factor C/EBPβ regulates IL-6 expression, and that it is crucial for mediating oncogene-induced senescence. Depletion of IL-6 reduced C/EBPβ expression and vice versa, suggesting that an interconnected feedforward loop operates between the genes encoding these proteins. The precise sequence of events downstream of IL-6 activity is undefined, but Kuilman and colleagues show that senescence driven by $BRAF^{V600E}$ depends, at least in part, on the induction of the tumour-suppressor protein $p15^{INK4b}$. However, another tumour suppressor, $p16^{INK4a}$ — a senescence marker in many cell types — seems to be dispensable for $BRAF^{V600E}$ response in fibroblasts.

The cytokine IL-8 also probably responds to oncogenic signals to drive premature senescence[2], specifically in benign tumours that express high levels of $p16^{INK4a}$. Like IL-6, IL-8 can promote senescence in a $p16^{INK4a}$-independent way in cultured cells[2]. It will be interesting to see whether that is the case *in vivo* — for example in the case of naevi (moles) driven by the $BRAF^{V600E}$ or RAS oncogenes, which may not necessarily induce the $p16^{INK4a}$ protein[6].

Acosta *et al.*[3] also show the possible impact of the secretory network on oncogene-induced senescence. In search of factors that extend the lifespan of human fibroblasts, these authors performed a functional screen using a library of short-hairpin RNAs. They find that CXCR2 — a receptor for several CXC chemokines, including CXCL1–7 and IL-8 — is a central mediator of senescence. Depletion of CXCR2 delayed not only senescence driven by oncogenes and DNA damage, but also natural senescence due to the shortening of telomere sequences at the ends of chromosomes.

The sequence of events leading to the