Figure 1 | PHD2 and tumour vasculature. Mazzone et al.[1] show that tumours grown either in normal mice or in mice lacking one copy of the *PHD2* gene (*PHD2*^{+/−} mice) show roughly similar growth rates and densities of blood microvessels. **a**, Yet in normal mice, tumours have disordered, poorly perfused blood vessels, which result in a low-oxygen environment and so intense VEGF production. **b**, By contrast, tumour vessels in *PHD2*^{+/−} mice look more like normal blood vessels, with the lining endothelial cells having a regular, flattened shape. These normalized vessels result in better oxygenation of the tumour, which in turn leads to less VEGF production and reduces these cells' response to VEGF by increasing expression of soluble and membrane-bound VEGR receptor-1, as well as VE-cadherin.

from perturbed oxygen sensing specifically in endothelial cells.

In principle, endothelial cells should be the last to experience hypoxia. Tumour cells often take on a cylindrical arrangement around blood vessels, with the most highly oxygenated cells closest to the vessels and hypoxic tumour cells farther away — adjacent to regions with no oxygen and so containing dying cells. Thus, Mazzone and colleagues' observation that endothelial cells contain oxygen sensors indicates that these cells, which are strategically located at the blood–tissue interface, act as gatekeepers for sensing oxygen levels. In agreement with this conclusion, the PHD-protein target HIF-2α is preferentially expressed in endothelial cells, and its role as an oxygen sensor of the vascular endothelium was reported previously[6].

Anti-angiogenic cancer therapy often prunes the most immature blood vessels in tumours to leave a thinned, more normal-looking vascular network of main blood vessels. This concept of 'vessel normalization' has received significant attention in recent years, not least because it helps to explain the clinically observed[7] synergy between anti-angiogenic and chemotherapeutic agents. The 'normalized vasculature' is better perfused and is thought to improve the access of chemotherapeutic drugs to tumours. Mazzone and colleagues' results suggest a mechanism by which this may occur.

Several molecular systems that act in concert have been implicated in vessel normalization, including the balance between VEGF, platelet-derived growth factor-B (ref. 8) and the vessel-destabilizing protein angiopoietin-2 (ref. 9). Mazzone et al. now add oxygen sensors to the list of factors regulating normalization of endothelial cells, and they propose that the manipulation of PHD proteins in these cells might have therapeutic potential. Although

a fascinating idea, therapeutic inhibition of PHD2 may be a long shot, as the mechanism underlying oxygen-sensing-dependent vascular normalization that the authors report is poorly understood.

For instance, Mazzone et al. implicate soluble and membrane-bound VEGF receptor-1 as well as VE-cadherin protein as PHD2-regulated mediators of endothelial-cell normalization. Although these molecules are major regulators of quiescent endothelial cells, they are not generally associated with angiogenesis-controlling, hypoxia-regulated genes. Moreover, it is surprising that Mazzone et al. did not find altered expression of molecules such as VEGF, angiopoietin-2 and its receptor Tie1 in endothelial cells of *PHD2*^{+/−} mice.

When thinking of hypoxia, one usually considers rapid adaptive response programs as being involved. So it could be that the tumour-vessel features seen in *PHD2*^{+/−} mice reflect long-term adaptation of endothelial cells to

the loss of one *PHD2* copy — a 'compensation' feature rather than an indication of a rapid loss of PHD2 regulation, as might be required from a therapeutic point of view.

On the basis of the vessel normalization observed in *PHD2*^{+/−} mice, Mazzone et al. describe endothelial cells lining a normalized vessel as 'phalanx cells'. At first sight, to rename a well-known cell — namely, the quiescent, resting endothelium — may seem unnecessary. Yet the introduction of the term phalanx cells comes at just the right time, and regarding them as such could significantly shape future research in vascular biology.

Angiogenesis research has focused strongly on the molecular and functional characterization of two cell types in an angiogenic sprout: the leading 'tip cell' and the subsequently proliferating and remodelling 'stalk cells'[10]. Although phalanx cells would conceptually seem to follow stalk cells, at present they are defined only functionally, as no molecular markers for them have been described. Better molecular characterization of phalanx cells might therefore greatly advance the field of vascular biology and pave the way towards cancer therapies that target activated endothelial cells. ■

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CHEMICAL PHYSICS

Melted in a flash

A. Cavalleri

The observation that atomic disorder emerges exceptionally fast during laser-induced melting of crystalline bismuth prompts fresh thinking about the nature of this phase transition.

In this issue (page 56), Sciaini et al.[1] report on the use of ultrashort bursts of electrons to observe the appearance of microscopic disorder when crystalline bismuth is melted by a laser. They find that melting occurs in less than 200 femtoseconds (one femtosecond is 10^{-15} s)

— a fraction of the period of an atomic-lattice vibration. This finding revisits a century-old debate about which microscopic properties map the solid and liquid phases onto one another.

The phase transitions we understand

best are those that can be pictured along a continuous, traceable trajectory connecting two known phases that differ mathematically by a single symmetry operation[2]. Liquid-to-gas transitions, in which microscopic order is absent from both phases, can be described in this way provided that the balance between attractive and repulsive forces between the atoms is known and that loss of symmetry is replaced by changes in density.

However, the description of solid-to-liquid transitions is not so trouble-free. The main problem is that when a crystalline solid melts, atoms not only become disordered, but also become free to move about in a network of weak bonds, which are constantly being broken and re-formed. The liquid must then be described not only by the relative positions of the atoms but also by their relative velocities. It is thus difficult to identify a mathematical procedure that maps out the transition between the solid and the liquid, one that describes both the loss of symmetry and the weakening of the bonds.

Some descriptions of melting have focused only on the emergence of structural disorder[3], and ignored the mechanical properties of the melt, akin to what would happen if a solid alloy were formed. Other theories describe melting only in terms of the vanishing of rigidity[4]. And indeed, a material in the solid phase, which is resistant to both compression and shear, loses its resistance to the latter when it melts. But this second description ignores the microscopic characteristics of the liquid phase, missing the key physics of disorder, entropy and the existence of latent heat (the amount of internal energy that must be 'traded in' for the increase in disorder).

Microscopic theories of melting are also hard to verify experimentally. The liquid phase does not emerge smoothly with increasing temperature, but rather switches on abruptly. At the melting temperature, randomly fluctuating nuclei of liquid grow and collapse incoherently at many sites in the atomic lattice at once. Melting then avalanches across the solid and the transition is over before one has had time to capture it. Understanding melting at the microscopic level thus requires following the changes associated with the phase transition on atomic lengths and timescales.

For some solids, excitation with optical lasers can weaken the bonds and trigger the transition simultaneously at all lattice sites. Although laser-induced melting does not necessarily follow the same pathway as the thermally driven process, it has the benefit of setting off the transition at a time and place chosen by the experimentalist, and reveals at least one possible microscopic pathway to melting.

In a stable, crystalline lattice of bismuth, moderate optical excitation is known to drive the lattice towards a higher-symmetry, cubic
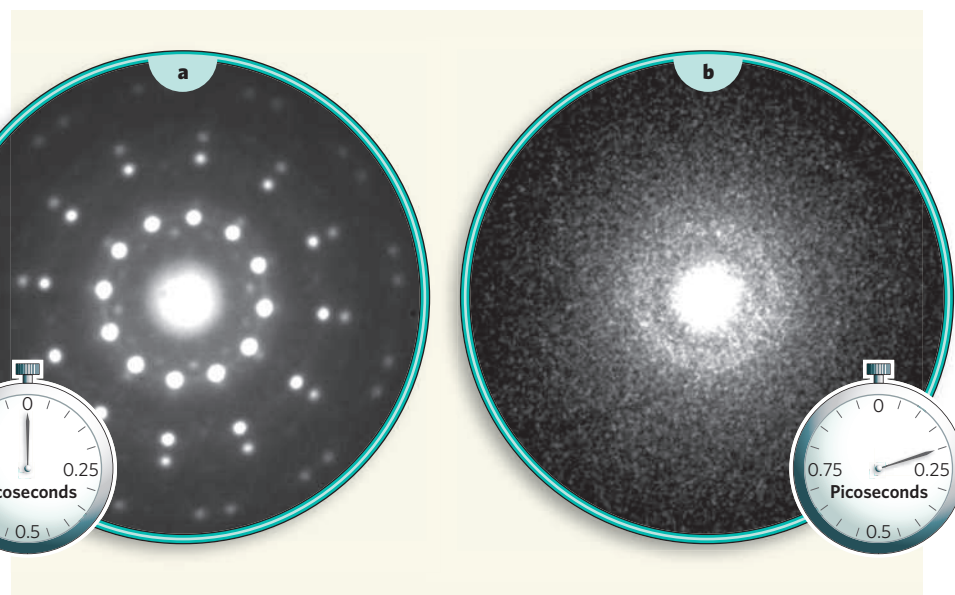
Figure 1 | Speedy melting. Sciaini *et al.*[1] irradiate crystalline bismuth with ultrashort bursts of electrons to monitor the emergence of atomic disorder during laser-induced melting. The images show electron-diffraction patterns observed before (**a**) and after (**b**) laser excitation. Atomic disorder emerges in about 200 femtoseconds (0.2 picoseconds). (Modified from a graphic by J. Harms.)

phase[5,6]. Interestingly, this intermediate cubic phase would not be stable at ambient pressures, and would be expected to melt away as a result of multiple collisions between atoms. This could be a tempting explanation for melting, one that involves the passage through an unstable atomic arrangement before atomic disorder occurs over a timescale of many atomic-lattice-vibration periods. Alternatively, intense optical excitation might simply cause the system to connect to the disordered phase in one go, driven 'downhill' by an internal force that has been unleashed promptly by the laser excitation[7,8].

Sciaini and colleagues[1] set out to test these hypotheses. In their experiments, they irradiated films of bismuth with laser pulses, comparing a wide range of laser intensities, and probed the films' atomic structures using ultrafast electron diffraction. This consisted of exposing the films to electron beams of femtosecond duration and taking snapshots of their atomic arrangements (Fig. 1). The authors find that disorder emerges at an increasing rate as the laser's intensity rises, reaching a point at which the sample effectively bypasses any intermediate state. Melting is found to occur within 190 femtoseconds — a fraction of the period of the atomic-lattice vibration.

But how does the laser-excited, ordered solid know how to become disordered without letting its atoms bounce around a couple of times to find the new ground state? Is it possible that the laser-excited solid acquires some aspects of the liquid phase before becoming disordered? Previous studies of phase transitions in semiconductors have already hinted that this could be the case[9]. So might we conclude that melting occurs before the atoms actually move? After all, a crystalline atomic arrangement would be a valid microstate of the liquid, just as good and as rare as any other. What would have to be liquid-like would be the forces between the atoms and the way the atomic velocities relate.

Or might we conclude that the disordered phase that emerges 200 femtoseconds after excitation is instead still rigid — that is, that the melt emerges only at longer times? The answer might lie in the ultra-fast real-time monitoring of the atomic-lattice-vibration frequencies, which could be achieved using fast optical or X-ray Raman scattering.

Our understanding of the dynamics of phase transitions will ultimately depend on our ability to measure both the positions of the atoms and the rigidities of the bonds. Some recent experiments indicate that such techniques may yield surprises[10]. Studies such as that performed by Sciaini and colleagues are not only tackling old questions with new technologies, but also prompting fresh questions about the multifaceted nature of the dynamics of matter. ■

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