environment. But are ultrahigh-resolution images of gaps between atoms useful for anything else?

I think the answer lies in the big success story of X-ray ptychography: tomography[4], a technique in which lots of 2D images of a transparent object are acquired as it is rotated, so that a 3D image can be built up. Phase information is an ideal imaging signal for this technique. But when images are taken through a solid object, the resolution needs to be as high as possible to distinguish features lying on the top surface from those at the bottom, many of which will seem (when seen in projection) to be laterally close to one another.

Jiang *et al.* tested the resolution of their electron microscope by putting two layers of atoms on top of one another and measuring the minimum apparent lateral distance between atoms in different layers, some of which were almost overlapping. In my view, this test demonstrates that their instrument could potentially be used for tomography. In theory, such imaging of multiple layers is not limited to crystalline 2D materials and could be used for any complicated, non-crystalline structure. Unfortunately, for thicker objects, the electron waves would scatter so strongly that they would spread out and re-interfere with each other in complicated ways, which would make it even harder — although in theory not impossible — to work out the structure.

Perhaps the take-home message of this work is not so much the record resolution, or its applications to 2D materials, but the fact that it will provide a way of precisely imaging the 3D bonding of every individual atom in a solid volume of matter, while using a minimal flux of damaging electrons. Indeed, the authors allude to this enticing possibility in their conclusions, suggesting that the next step is to use their remarkable detector for tomography. The aim would then be to solve the exact 3D atomic structures of solids that have no long-range order, such as nanocrystalline materials, glasses and amorphous metals, for which we must currently infer structures from averaged bulk measurements. ■

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CARDIOVASCULAR BIOLOGY

Cells stop dividing to become arteries

An analysis of gene-expression patterns in single cells provides detailed insights into the developmental processes that lead to maturation of the coronary arteries. SEE ARTICLE P.356

ARNDT F. SIEKMANN

The human heart pumps between about 5 and 20 litres of blood through the body every minute[1]. To receive enough oxygen to fulfil this tremendous task, heart-muscle cells need their own blood supply. This is provided by specialized blood vessels, including coronary arteries. Defects in these arteries can lead to coronary heart disease and even heart attack[2,3]. Understanding how coronary arteries form during embryonic development is therefore of great interest, because such knowledge might help in developing strategies to prevent or treat coronary heart disease. On page 356, Su *et al.*[4] provide a detailed picture of the sequence of events that leads to coronary artery development.

The cells that generate coronary arteries originate from various regions of the embryo, including a sac-like structure called the sinus venosus that adjoins the embryonic heart[5,6]. From these sites, the cells invade the heart's muscle-cell layer. Here, they form an immature blood-vessel network called a plexus that is subsequently remodelled into functional arteries and veins.

Su and colleagues set out to investigate how cells from the sinus venosus develop into coronary arteries, using single-cell RNA sequencing (scRNA-seq) — a technique that enables precise identification of the genes being expressed in each cell of a tissue[7]. Gene-expression patterns change during tissue differentiation, for example as sinus venosus cells mature into coronary arteries. Comparison of the gene-expression patterns for individual cells of a given type can therefore reveal the cells' relationships to one another.

The authors extracted single endothelial cells, which make up the inner lining of blood vessels, from the hearts of mouse embryos at a developmental time point just before coronary artery formation. They reasoned that, at this embryonic stage, they would obtain cells at the various stages leading to coronary artery maturation, including sinus venosus and plexus cells. They then used bioinformatics to investigate the lineage relationships between these cells.

It has been thought that the remodelling of

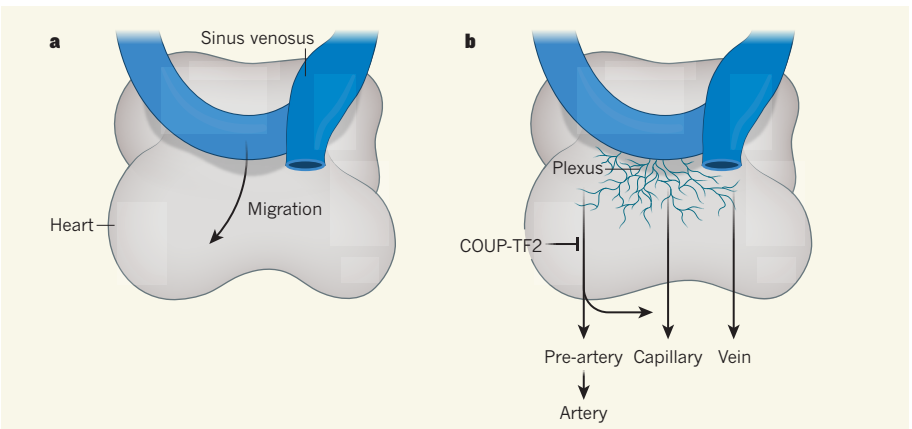

Figure 1 | Coronary artery development starts early. **a**, During the development of mouse embryos, cells from a sac-like structure called the sinus venosus migrate into the muscle-cell layer of the heart. **b**, There, they give rise to an immature blood-vessel network (a plexus), which will be remodelled to form arteries, veins and capillaries. Su *et al.*[4] have shown that a subpopulation of immature plexus cells, which the authors dub pre-artery cells, have a gene-expression profile that is characteristic of mature arteries. The transcription factor COUP-TF2 prevents plexus cells from adopting this profile. Pre-artery cells predominantly give rise to mature coronary artery cells, although a few become part of capillaries instead. (Figure adapted from Fig. 4h of ref. 4.)

the plexus into arteries and veins starts only after the plexus has connected to the aorta (the main heart artery), and therefore after the onset of blood flow[5]. But, unexpectedly, Su *et al.* found that several cells from their embryos, in which the plexus had not yet received blood, had a gene-expression profile associated with mature arteries. They called these cells pre-artery cells.

The authors used a genetic strategy to indelibly label the pre-artery cells with a marker protein, such that these cells and the lineages they give rise to could be tracked during embryonic development. This lineage tracing revealed that, although most pre-artery cells did go on to form coronary arteries, some were incorporated into capillaries, which connect coronary arteries with veins. Thus, it seems that, although certain endothelial cells are genetically predisposed to form arteries, they also have a degree of developmental plasticity (Fig. 1).

Next, Su and colleagues performed a detailed analysis of the gene-expression patterns of cells on the developmental spectrum from sinus venosus to pre-artery cells. Changes in gene expression towards more arterial-like profiles occurred only gradually along most of the spectrum. However, there was a sharp change as cells crossed a threshold to adopt a pre-artery state. The researchers showed that the greatest difference in expression in pre-artery cells compared with other cells in their analysis occurred in genes implicated in regulating the cell cycle. Furthermore, in mouse embryos, pre-artery cells proliferated less than did cells in the plexus. Thus, limiting cell divisions might be a prerequisite for coronary artery maturation.

Indeed, the authors found that overexpression of the transcription factor COUP-TF2 in mice inhibited pre-artery formation by upregulating cell-cycle genes. COUP-TF2 was previously thought to limit the growth of arteries by suppressing the Notch signalling pathway[8]. But Su *et al.* showed that activation of Notch signalling could not prevent the defects caused by COUP-TF2 overexpression in mouse embryos. By contrast, pharmacological inhibition of the cell cycle increased artery formation in an *ex vivo* experiment. Thus, COUP-TF2 has functions in artery development that are independent of Notch signalling. Together, Su and colleagues' work provides exciting insights into coronary artery formation. It will be interesting to discover whether the findings apply to artery development in other settings.

It will also be valuable to delineate the signalling pathways that lead certain cells to adopt the gene-expression profile of pre-artery cells. The Notch signalling pathway, acting independently of COUP-TF2, is a prime candidate. Studies in several developmental settings[9–11] have suggested that new blood-vessel sprouts initially emanate from veins and capillaries and only subsequently form arteries, with each activity inhibiting the other. Inhibiting Notch signalling can lead to excessive blood-vessel sprouting, while at the same time preventing artery formation[12,13], and a similar effect is seen during coronary artery development[14]. It will therefore be interesting to investigate how Notch signalling affects the gene-expression profiles that lead to the formation of pre-artery cells.

Although it is becoming increasingly clear that artery differentiation is intimately linked to cell-cycle state, the underpinnings of this relationship need further investigation. A report last year showed that cell-cycle inhibition is important for proper arterial gene expression in cells *in vitro*[15]. In addition, the signalling pathways involving Notch and vascular endothelial growth factor, which are indispensable for the establishment of new blood-vessel networks, are both implicated in influencing endothelial-cell proliferation[16]. However, it is not known how cells interpret signalling inputs from these pathways to balance the demand for proliferation of cells in the blood-vessel network with the need to establish new arteries.

One must also bear in mind that cell-lineage trajectories obtained from scRNA-seq might not reflect true developmental relationships. For instance, cells that have similar gene-expression patterns are not necessarily derived from the same precursor population. New techniques that unite cell-lineage tracing with scRNA-seq[17] will help to bridge this gap, and will surely provide further insights into coronary artery development. ■

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GENOMICS

Newfound differences between great apes

High-quality genome sequences for some of the great apes have been assembled using state-of-the-art sequencing tools. The assemblies provide an unbiased comparison between humans and their closest evolutionary relatives.

AYLWYN SCALLY

Much of evolutionary biology is motivated by the principle that you cannot understand one species without comparing it with another. When nineteenth-century naturalists compared the anatomies of humans and other apes, it became clear that these species shared many features and had evolved from a common ancestor. More recently, developments in DNA sequencing — which enabled assembly of the human genome[1] in 2001, followed by lower-quality 'draft' genomes for other great apes[2–4] — have transformed our understanding of this evolutionary process. Writing in *Science*, Kronenberg *et al.*[5] describe new great-ape genome assemblies, generated using a technology that surpasses previous methods. This work marks a new stage in our ability to study and compare these species.

Genome assembly is often likened to piecing together a jigsaw puzzle — a huge jigsaw for which the box has been lost and we have only a vague idea of what the whole should look like. The analogy holds because sequencing technologies cannot sequence an entire chromosome in one go. Instead, they fragment the genome into many separate pieces, called reads, which have to be matched, overlapped and placed together.

Previous generations of sequencing machines produced reads that were only about a hundred base pairs long, or perhaps a thousand base pairs but at exorbitant cost. Current machines such as Pacific BioScience's single-molecule real-time (PacBio SMRT) sequencer produce reads tens of thousands of base pairs in length. Even with this improvement, hundreds