overcome the entropic penalties associated with the self-assembly of large cages, and to avoid the unwanted but faster formation of smaller cages.

Are there likely to be any practical applications for these giant cages? Investigations into the chemistry and properties of such assemblies might be severely hampered by the difficulties in synthesizing them, especially in bulk quantities rather than just as individual crystals. The structural integrity of the cages, both in solution and in the solid state, is also an unknown crucial issue for any applications. Nevertheless, these huge metal–organic assemblies might encapsulate giant biomolecules such as proteins by forming host–guest interactions, thus stabilizing the biomolecules and potentially allowing control of their structures in unnatural conditions.

Apart from their value as benchmarks for artificial self-assembly processes, Fujita and co-workers' structures might also inspire interest from other scientific areas. For instance, mathematicians could seek more-exotic topologies as targets for self-assembly, and biologists might search for previously unsuspected topologies in virus capsids or other large biological assemblies. And only time will tell whether Fujita and colleagues' synthetic masterpiece will be the starting point for further journeys into yet-unexplored chemical territory. ■

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CARDIOVASCULAR DISEASE

A turbulent path to plaque formation

Plaque deposits often occur in curved arterial regions with turbulent blood flow. Endothelial cells have been found to respond to blood flow through a previously unidentified signalling pathway that affects plaque build-up. SEE LETTER P.579

VEDANTA MEHTA & ELLIE TZIMA

A key characteristic of the disease atherosclerosis is the gradual accumulation of plaque deposits on the walls of arteries. Plaque is composed of cellular waste, fatty deposits and cholesterol molecules, and is not uniformly distributed in arteries[1]. Some plaques can reach a size that obstructs blood flow to organs, causing heart attacks or strokes[2]. On page 579, Wang *et al.*[3] propose a mechanism for plaque development that also provides an explanation for plaque-formation patterns.

Blood-flow dynamics have a central role in atherosclerosis development, and the key driving force is shear stress[4]: the frictional force exerted on blood-vessel walls because of blood flow. Shear stress as a result of the uniform laminar blood flow that occurs in straight regions of blood vessels is not considered to be a risk factor for plaque formation[4]. However, curved blood-vessel regions, including those near branch points, have disturbed (turbulent) blood-flow patterns and are more susceptible to plaque development[4].

How do differences in the mechanical forces exerted on blood vessels result in the promotion or inhibition of plaque formation? Endothelial cells line blood-vessel walls and can sense and distinguish laminar and disturbed blood-flow patterns, which results in changes to endothelial signalling pathways that ultimately determine whether plaque formation is promoted or inhibited[4].

YAP and TAZ proteins act as cellular sensors or checkpoints for mechanical forces[5]. These proteins are also master regulators in the Hippo-protein-mediated signalling pathway, which controls organ size and has a tumour-suppressor function[6]. In atherosclerotic arteries, two of the genes transcribed through the actions of YAP and TAZ are highly expressed[7,8]; however, direct evidence that links YAP and TAZ to the sensing of mechanical force by endothelial cells and to the development of atherosclerosis has been lacking.

Activation of the YAP and TAZ pathway can be measured by assaying phosphorylation of YAP, movement of the proteins into the nucleus or the expression of their target genes. Using all three assays, Wang *et al.* observed the inhibition of YAP and TAZ activity when endothelial cells grown *in vitro* were subjected to uniform, laminar shear stress. By contrast, YAP and TAZ activity was high when these cells were exposed to disturbed shear stress (Fig. 1).

Wang and colleagues confirmed that YAP and TAZ activity is regulated by blood flow, using an *in vivo* system in which the abdominal

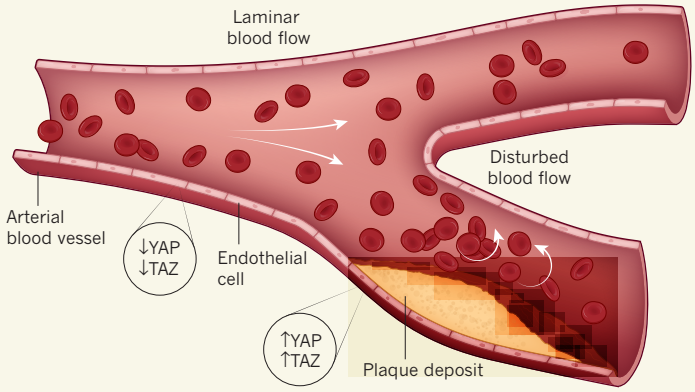

Figure 1 | Endothelial-cell signalling can affect plaque formation. Laminar blood flow parallel to the blood-vessel wall usually occurs in straight regions of arteries. Disturbed, non-laminar blood flow occurs in curved arterial regions, including those near where a vessel branches. The endothelial cells that line blood vessels can sense and respond to these two different types of blood flow[4]. Regions of disturbed blood flow are associated with deposits of plaque, an accumulation of cellular waste and fatty molecules that can obstruct blood flow and potentially cause disease. Wang *et al.*[3] report that, in experiments using mouse models and human tissue, endothelial cells adjacent to disturbed blood flow had high YAP and TAZ activity and increased plaque formation. By contrast, endothelial cells adjacent to laminar blood flow have low YAP and TAZ activity and do not have plaque deposits.

artery in rats is clamped. This constriction generates regions of uniform and disturbed shear stress in the same blood vessel[9]. High YAP activity was observed where blood flow was disturbed, and low YAP activity was seen in a region subjected to high uniform shear stress.

To determine whether their findings were relevant to atherosclerosis *in vivo*, Wang and colleagues used a mouse model of atherosclerosis. These animals lack a protein that affects cholesterol metabolism and are susceptible to plaque formation when fed a high-fat diet[10]. The mice that developed atherosclerotic plaques had high YAP and TAZ activity in their arteries. The authors also examined samples of human atherosclerotic blood vessels and saw similar high YAP and TAZ activity.

The authors then tested whether manipulating the level of YAP affects plaque formation. Using a version of the atherosclerotic mouse model in which YAP was overexpressed in endothelial cells, they observed that, after four weeks on a high-fat diet, the mice had significantly increased plaque formation as compared with control animals.

To determine the role of YAP in atherosclerosis mediated by disturbed blood flow, the authors subjected atherosclerotic mice[10] to disturbed shear stress through surgery to the carotid artery[11]. In this system, mice that had also been genetically engineered to have lower endothelial YAP expression had significantly less atherosclerosis than did control animals. Lower atherosclerosis, as compared with control mice, was also seen if the gene expression of TAZ rather than YAP was decreased.

Wang *et al.* propose that the laminar-shear-stress pathway that inhibits YAP and TAZ comprises several molecules that participate in the process of mechanotransduction — the mechanism by which cells convert mechanical signals into biochemical responses. The authors found that laminar shear stress promotes the activation of integrin proteins, promotes the interaction between integrin β_3 and the $G\alpha_{13}$ protein and inhibits the protein RhoA, and that these signalling changes subsequently lead to YAP inactivation. Integrin β_3 also has a plaque-promoting role[12–14], but how this relates to the plaque-inhibiting role identified by Wang and colleagues is unknown and needs to be investigated.

To explore the plaque-promoting signalling pathways associated with YAP and TAZ activation, Wang and colleagues conducted cellular analyses, including the analysis of messenger RNA sequences. This revealed that YAP and TAZ promote the activation of several inflammatory pathways, including the atherosclerosis-promoting JNK-protein pathway. It is well established that atherosclerosis is a multifactorial disease in which inflammation has a crucial role.

Drugs that lower cholesterol to prevent plaque formation are the most commonly prescribed medicines in Western countries, and are a first-line therapy for people who have cardiovascular disease. Cholesterol-lowering statin drugs regulate the YAP and TAZ pathway[15,16]. Whether these drugs protect against plaque formation through modulation of the YAP and TAZ pathway was unknown.

Wang and colleagues treated human cells that express constantly active YAP and TAZ *in vitro* with the statin simvastatin. They found that the treatment did not suppress YAP/TAZ-dependent expression of key genes that promote inflammation and atherosclerosis, indicating that the anti-inflammatory and anti-plaque effects of statins are probably mediated by inhibition of YAP and TAZ activity. This indicates that the YAP and TAZ pathway could be considered as a treatment target for atherosclerosis.

Atherosclerosis is a complex disease in which associated inflammation probably occurs through several different pathways, and this complexity presents an obstacle to successful clinical treatment. Is it possible to target YAP and TAZ specifically in endothelial cells in the arteries? Is suppression of just YAP and TAZ, or the molecules within the YAP and TAZ signalling pathway, sufficient to ameliorate atherosclerosis? Does targeting the pathway also affect the tumour-suppressing function of the Hippo pathway? These questions need to be answered before a therapy to prevent atherosclerosis can be devised on the basis of YAP and TAZ inhibition. ■

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BIOMATERIALS

Sharks shift their spine into high gear

It emerges that a dogfish shark's spine becomes stiffer as the fish swims faster, enabling the animal to swim efficiently at different speeds. The finding could also provide inspiration for the design of robotic biomaterials.

MATTHEW A. KOLMANN & ADAM P. SUMMERS

The languorous undulation of a shark cruising along a reef gives little hint of the fish's potential to unleash a burst of high-speed movement when pursuing prey. Writing in the *Journal of Experimental Biology*, Porter *et al.*[1] reveal how the structural properties of the non-bony, cartilaginous skeleton of the spiny dogfish shark (*Squalus acanthias*) allow this fish to shift seamlessly between low-speed cruising and high-speed swimming.

A basic principle of aquatic locomotion is that swift swimming requires a stiff spine[2]. A stiffer body decreases drag and increases energy efficiency (Fig. 1). By contrast, acceleration requires a flexible spine to allow a fish to uncurl its body in a sudden rush[3]. It was proposed[2] that thick fibres in a shark's skin increase the stiffness of the fish as it swims faster. This hypothesis is attractive, but has resisted experimental verification because of the difficulty of getting sharks to swim fast in a laboratory while attached to high-tech instrumentation.

Porter *et al.* investigated shark propulsion from a different direction. Rather than considering the fish's exterior, they went right to the core of the matter: the vertebral column, or spine. In bony animals, the vertebrae of the spine are mineralized, rigid, bony structures that do not change shape appreciably during locomotion. Movement of the spine in bony animals occurs through changes in the shape of the intervertebral disks — elastic, but quite firm structures located between individual