Chan *et al.* showed that asynthetic fission peaks during the rapid expansion phase of larval development, when the need for increasing epithelial coverage is at its highest. In addition, they found that asynthetic fission can be triggered during tissue regeneration after a fin amputation. The authors also experimentally manipulated the growth rate of larvae by rearing them at different densities (the more fish there are in a given volume of water, the lower the growth rate). This manipulation led to changes in the division rate of SECs. Together, these data indicate that asynthetic fission can provide a flexible way to adjust the epithelial surface area.

The authors observed that the total volume of the four daughter cells matches that of the initial mother cell. Keeping this in mind, they predicted, using a simple mathematical model, that asynthetic divisions have the potential to efficiently increase SEC surface coverage. Surprisingly, however, one cell division takes longer than basal epidermal-cell mitosis. Thus, an intriguing question remains — what is the advantage of asynthetic fission compared with a mechanism by which non-dividing cells are stretched and flattened to increase their coverage area? One probable answer is that cell divisions that occur in the direction of stretch rapidly reduce mechanical tissue tension, as has been demonstrated in mammalian cell cultures[10] and early zebrafish embryonic development[11].

On the basis of previous work linking epithelial stretch and growth[2], the authors hypothesized that the build-up of tissue tension created by organismal growth could control asynthetic fission. One major group of tension sensors is mechanosensitive ion-channel proteins such as Piezo1 (ref. 12). Chan *et al.* found that experimental activation of Piezo1 led to a significant increase in asynthetic fission in SECs, whereas inhibition of *Piezo1* gene expression attenuated division. This indicates that the asynthetic fissions could be controlled by Piezo1-mediated stretch sensing. Interestingly, larvae in which *Piezo1* was inhibited showed normal body-growth rates despite the lack of asynthetic division. It would be interesting to know whether the division rate of basal progenitor cells is increased in these animals, as a compensatory mechanism to produce excess cells, or whether other adaptive growth mechanisms kick in.

It will be essential to understand the mechanisms of asynthetic fission in more detail. Chan *et al.* show that chemical inhibition of cell-cycle checkpoints, or of the enzymes that regulate them, does not strongly influence asynthetic fission. However, the negative systemic effects of these drugs prevented the authors from studying their effect on SECs for more than a few hours. In future, analyses involving genetic manipulation of cell-cycle regulators specifically in SECs could help to determine whether this mode of division is truly independent of cell-cycle regulation and checkpoints. In addition, the molecular mechanisms triggered by Piezo1 signalling in SECs remain to be determined. Finally, whether this mechanism is used in other tissues and organisms is a fascinating open question.

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Atherosclerosis

# Nerve remodelling at a distance

**Courtney Clyburn & Susan J. Birren**

Fatty structures called plaques can form in arteries, and are separated from nerves by the artery walls. But this is no barrier to communication — it seems that nerves interact with plaques and immune cells to drive cardiovascular disease. **See p.152**

The insidious accumulation of fatty structures called plaques on the inner walls of arteries wreaks havoc on the cardiovascular system, narrowing the vessels, reducing blood and oxygen delivery to crucial organs, and causing heart attacks and strokes[1]. Inflammation, triggered by immune cells, has been recognized as a major factor in plaque formation[2], bringing hope of new interventions against disease. Mohanta and colleagues[3] strengthen this hope even more on page 152, identifying tripartite interactions between nerves, immune cells and plaques as a key component of atherosclerosis — a life-threatening disease that affects millions of people[1]. When these interactions are disrupted, plaques shrink and plaque-associated immune structures are destabilized, suggesting that this unexpected crosstalk could be targeted to treat atherosclerosis.

Atherosclerotic plaques form when lipoproteins and immune cells accumulate on the inner surfaces of arteries. Immune cells in these plaques — such as macrophages, which are part of the innate immune system — initiate inflammatory signalling cascades, causing other immune cells, known as leukocytes, to infiltrate the outer arterial layer (the adventitia). Adventitial immune cells accumulate near the plaques, forming tertiary lymphoid organs that provide a platform for the amplification of inflammation. Strategies for treating atherosclerosis by dampening inflammation look promising, but progress is hampered by the complexity of the immune responses.

Until now, it was assumed that the nervous system was not involved in atherosclerosis, because the vessel wall physically separates plaques from nerve fibres. However, the peripheral nervous system (the nerves that communicate with, but are outside, the brain and spinal cord) uses the adventitia as a conduit for reaching peripheral targets, and there is evidence that fibres directly innervate the smooth muscle of blood vessels[4]. This led Mohanta and colleagues to an exciting realization: in atherosclerosis, aggregates of immune cells infiltrate the outer vessel layer that also contains peripheral fibres. This factor — together with accumulating evidence for inflammation-dependent plasticity of neurons of the peripheral and central nervous systems[5] — prompted the authors to investigate whether the peripheral nervous system interacts with plaque-associated adventitial immune cells, allowing plaques to drive neural remodelling from a distance.

The authors set out to identify differences in nerve fibres in plaque-laden and plaque-free arteries. Using extensive imaging, they evaluated the density and chemistry of neurons in plaque-burdened and plaque-free segments in a mouse model of atherosclerosis (mice lacking the *Apoe* gene), as well as in other rodent models of atherosclerosis and in human

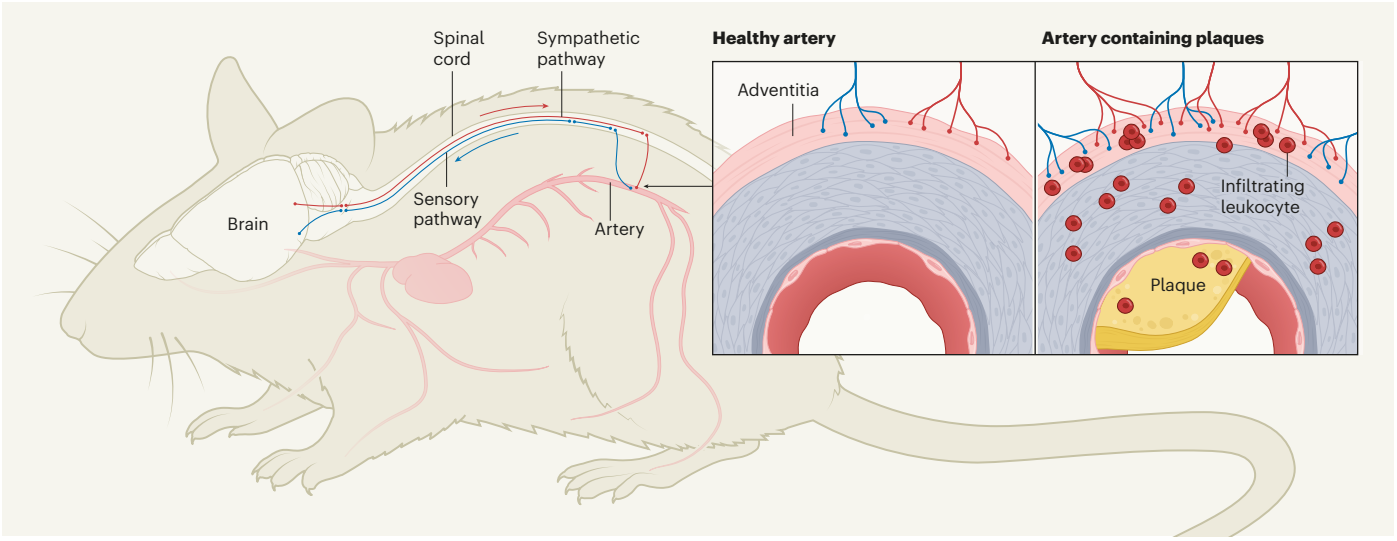


**Figure 1 | Neuroimmune–cardiovascular interactions drive plaque formation.** In healthy arteries, sensory (blue) and sympathetic (red) nerves are found in the adventitia (the artery outer layer). In arteries containing fatty build-ups called plaques, immune cells known as leukocytes infiltrate the inner plaque and through the arterial wall to the adventitia. Mohanta *et al.*[3] find an increased density of both sensory and sympathetic nerve fibres in these plaque-laden regions. The authors suggest that plaque-induced activation of sensory neurons in the adventitia leads to activation of sympathetic nerves in the brain. This, in turn, drives heightened activity and increased density of sympathetic projections to the artery, promoting further growth of plaques.

tissue. They found that the density of fibres increased substantially in plaque-burdened segments (Fig. 1). These fibres comprised both sensory neurons (which send sensory information to the brain) and sympathetic effector neurons (which transmit information from the brain to the organs). Strikingly, plaque size correlated strongly with fibre density.

These data suggest that plaques might act through the arterial barrier to drive neural remodelling. The authors compared gene expression in *Apoe*-mutant mice and controls, and found tantalizing hints of possible molecular drivers of this process – including nerve growth factor and lymphotoxin-β, a protein involved in the formation of vascular immune-cell structures[6]. The wealth of information generated by the authors' gene-expression analyses will enable researchers to pin down the specific plaque or immune-cell factors responsible for neural remodelling.

**"The neuroimmune interactions described by the authors have analogies in other diseases, such as heart attack and cancer."**

The findings raise the question of what role neural activity might have in the progression of atherosclerosis. To answer this question, Mohanta *et al.* reduced the excessive sympathetic innervation of the adventitia in *Apoe*-mutant mice through two experimental methods – chemically disrupting sympathetic fibres by administering the drug 6-hydroxydopamine, and physically removing the nerve bodies of the coeliac ganglia (abdominal clusters of sympathetic-nerve cells from which the fibres originate). Both treatments reduced the density of sympathetic nerve fibres and the levels of the sympathetic neurotransmitter molecule noradrenaline, as well as causing the collapse of immune-cell structures associated with plaques. After coeliac ganglion removal, plaque volumes also shrank – potential evidence for neural regulation of plaque progression.

Given that sympathetic nerves rely on noradrenaline-mediated (noradrenergic) signalling, these findings suggest that clinical strategies to reduce this neurotransmitter's actions might slow the development of atherosclerosis. As well as reducing noradrenaline levels, however, these experimental methods abolish the release of other neural signalling molecules. It will be important to establish the contributions of these other factors by directly blocking noradrenergic signalling. There is evidence that beta-blockers, drugs that specifically inhibit the activity of adrenergic-receptor proteins, slow disease progression in atherosclerosis[7]. But this work has been complicated by the need to understand possible indirect effects of the drugs on associated cardiovascular disorders. This previously unknown plaque–immune–nerve interface now provides a target structure – as well as a theoretical framework – for analysing the effects of beta-blockers.

Do neuroimmune–cardiovascular interfaces extend beyond the plaque-burdened adventitia? Mohanta *et al.* showed that peripheral-neural structures located some distance from plaques (such as the coeliac ganglia) are also infiltrated by immune cells. The authors then investigated whether this signalling was integrated at the level of the brain. They defined the central neural circuits associated with atherosclerotic structures by injecting a 'retrograde' virus into the tertiary lymphoid organs associated with plaques, and tracing the virus's passage along connected neurons. This revealed an extensive artery–brain circuit, with distinct sensory and sympathetic arms. Imaging of the activity of brain neurons in this circuit suggested that brain activity contributes to atherosclerosis.

The authors suggest an attractive model in which plaque-induced activation of sensory neurons on the adventitia leads to activation of sympathetic centres in the brain, in turn driving heightened activity and increased density of sympathetic fibres in the periphery. The resulting increased release of noradrenaline promotes plaque growth. Further work is needed to determine the importance of such a centrally driven, aberrant feedforward cycle, compared with a more-localized model in which increased sympathetic activity might stimulate immune cells through β-adrenergic receptors. This might not only enhance plaque formation, but also result in the release of factors that further drive peripheral sympathetic-neural activity[8]. Identifying the correct model will require the use of genetic engineering to silence various branches of the neural pathways.

The neuroimmune interactions described by Mohanta and colleagues have analogies in other diseases, such as heart attack and cancer. Injury to the heart muscle leads to inflammation and infiltration of macrophages into the muscle, where macrophage-derived nerve growth factor leads to increased density of sympathetic nerves[9]. Similarly, invasion of the tumour microenvironment by nerve fibres

results in immune activation, growth of new blood vessels and modulation of tumour progression[10]. These neuroimmune interactions involve a mix of sensory, sympathetic and parasympathetic nerves that modify disease progression through direct interactions with affected tissue and the immune system.

Mohanta and colleagues' discovery that neuroimmune signalling also contributes to atherosclerosis is a valuable contribution to the field. The interactions that they have uncovered also feature a twist, in which atherosclerotic plaques remodel sympathetic and sensory nerves from a distance and through a barrier. The findings not only suggest new directions for research into possible treatments, but also raise the prospect that distant neural remodelling across barriers occurs in other organs and diseases — including those not generally thought to have a neural component.

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Food production

# Environmental benefits of eating mycoprotein

**Hanna L. Tuomisto**

Would environmental damage be reduced by replacing beef with mycoprotein produced in cell culture? Modelling shows that this change could greatly cut global deforestation, pasture area and greenhouse-gas emissions. **See p.90**

The development of alternatives to animal-sourced foods has increased during the past few decades as a response to the negative environmental impacts of livestock production. These alternatives include foods that are produced by the industrial-scale culture of animal, plant and microbial cells. Studies have shown that, per unit of mass, cell-cultured foods can have a lower environmental footprint than that of proteins from livestock[1], but comparisons of global-level assessments have been lacking. On page 90, Humpenöder *et al.*[2] report the first global analysis of the environmental benefits that could be achieved by substituting beef with mycoprotein from cell culture.

Cell-cultured foods are produced by cultivating cells in bioreactors — usually, steel tanks — containing nutrients and other factors needed for cell growth. The cultivated cells can be used either directly as food or to synthesize substances (such as proteins or fatty acids) that make up food ingredients[3]. Most cell types source their carbon from glucose, which is generally obtained from agricultural crops, although some microbial cells can obtain carbon from methane or carbon dioxide[4]. Cropland is therefore required to produce feedstocks for most cell-cultured foods.

Humpenöder *et al.* investigated the environmental impacts of replacing beef with mycoprotein[5]. Many cell-cultured food products are still in development, but mycoprotein-based products are already widely available in supermarkets in many countries. Mycoprotein is an ideal substitute for meat because it is rich in protein and contains all the essential amino acids that humans obtain from nutrition. The products are textured and shaped to resemble common meat products, including processed foods (such as sausages and burger patties) and ingredients for cooking (such as minced beef or chicken breast).

The authors modelled the changes in land use, greenhouse-gas emissions, water use and nitrogen fixation (the biological process by which nitrogen gas is converted into compounds that can be used as nutrients by other organisms) that would result from replacing 20%, 50% and 80% of global beef consumption with mycoprotein. They used a 'middle of the road' socio-economic scenario as a baseline for estimates of the increases in population, income and livestock demand between 2020 and 2050. Their assessment of the environmental impact of mycoprotein culture considered the cultivation of sugar cane as a source of glucose, but ignored the effects of producing other nutrients and the energy required for the cell-culturing processes. In effect, the study therefore simply compared the land-use impacts of beef and sugar-cane production. The estimated quantity of sugar cane produced was based on the glucose requirements of culturing an amount of mycoprotein equivalent to that of the beef protein being replaced.

The modelling shows that the increase in beef consumption in the baseline scenario would require expansion of global pasture and cropland areas, causing a doubling of the annual deforestation rate between 2020 and 2050. Substituting 20% of beef consumption with mycoprotein halves the annual deforestation rate (Fig. 1). Over the same period, the scenarios assuming 50% and 80% substitution levels result in a decline in global pasture area and substantial reductions in annual deforestation rates.

The relationship between the percentage of beef substitution and the annual deforestation rates in 2050 is nonlinear. Because the pasture area required in 2050 at the two highest substitution levels is lower than that

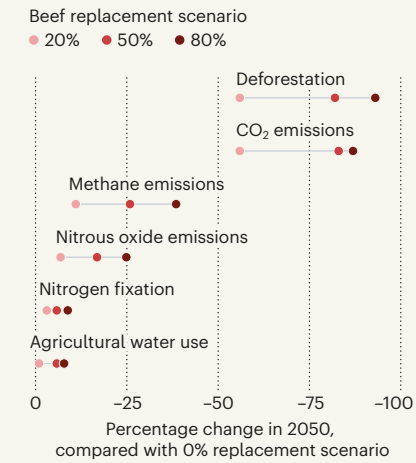


**Figure 1 | Modelling the effects of switching from beef to mycoprotein consumption.** Humpenöder *et al.*[2] estimated the global environmental impacts associated with replacing 20%, 50% and 80% of beef in people's diets with mycoprotein. In 2050, the substitutions have a large effect on deforestation and carbon dioxide emissions; a modest impact on emissions of methane (a greenhouse gas) and nitrous oxide (a gas pollutant associated with agriculture); and only a small effect on nitrogen fixation (the biological process by which nitrogen gas is converted into forms of nitrogen that can be used as nutrients by other organisms) and agricultural water use. (Adapted from Fig. 3g of ref. 2.)