used a combination of approaches centring on a model system for plant-membrane studies comprising the developing eggs (oocytes) of the African clawed frog *Xenopus laevis*, and lipid vesicles (termed liposomes) generated *in vitro*.

The authors demonstrated that effector expression in *X. laevis* oocytes promoted ion currents across the cell membrane, as well as swelling and bursting of the cells dependent on solute concentration (osmolarity) and passive uptake of a fluorescent dye, all of which were consistent with a channel function. Moreover, although the presence of the effector protein in liposomes containing a fluorescent dye resulted in release of the dye, liposomes containing a fluorescent protein that was larger than the predicted size of the channel did not release the fluorescent protein.

Collectively, the authors' results indicate that AvrE/DspE-family effectors function as water- and solute-permeable channels in the cell membranes of eukaryotes (organisms that have a nucleus). These are among the first known effectors of plant-targeting bacteria to exhibit a direct cellular function in plant cells, rather than operating through host proteins. The findings add to a growing body of evidence that manipulation of apoplastic water is a primary control point for pathogens.

The study also demonstrates an exciting application of these findings in managing bacterial plant diseases. The authors predicted the channel diameter and identified chemicals that were then engineered to block the channels. These synthetic compounds not only inhibited the channel activities of the effectors in *X. laevis* oocytes, but also reduced or eliminated plant infections by two bacterial pathogens. AvrE- and DspE-mediated infections by *Pseudomonas syringae* pv. *tomato* on the model thale cress plant *Arabidopsis thaliana* and *Erwinia amylovora* (fire blight) on pear fruits were inhibited, respectively. These findings provide a new and potentially effective management strategy for bacterial pathogens. Moreover, by targeting an activity required for plant infection but not for bacterial growth, as such, channel blockers of this type should avoid favouring the emergence of drug-resistant pathogens, as occurs with antimicrobial treatments.

The authors have identified a key pathogen factor that helps to combat the limited water availability in the apoplast and therefore promote bacterial growth. A major unresolved question is how these proteins actually manage to modulate water and solute movement to generate a suitable aqueous environment in the apoplast. Answering this question will require a better understanding of the dynamics of water and solute gradients across the cell membrane of plants. The discovery of similar effectors made by eukaryotic pathogens called oomycetes[8] raises the question of whether other plant-targeting pathogens also use such channels during infection.

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Polymer chemistry

Waste product from wood finally used to make glue

Charles E. Frazier

Scientists have had limited success in converting lignin, a structural component of plants, into high-value products. The discovery that lignin can be used as a wood glue could be a game-changer for biorefineries. **See p.511**

On page 511, Yang *et al*.[1] describe a remarkable strategy for making a wood adhesive from lignin – the extraordinary polymer that strengthens and binds together plant cells. Lignin waste streams (known as technical lignins), currently generated from wood pulp and paper production, are notoriously ineffective for making adhesives of the required performance and at the scale needed for manufacturing wood composites. Now, for the first time, a lignin waste stream can be used as a high-value feedstock for manufacturing wood adhesives and other products. Furthermore, the findings could pave the way for a new generation of integrated plant-processing biorefineries – facilities that process biomass, such as agricultural waste, trees and grasses, with high efficiency to produce renewable energy, chemicals and other products.

Lignin enables trees to reach grand heights and prevents maize (corn) stalks from buckling in the wind. Plants use lignin to protect cellulose, the major part of non-edible plant matter. Cellulose consists of polymeric chains of linked glucose molecules, and assembles into long, stiff and exquisitely uniform fibres, which plants use to make their structures. Nearly all of Earth's organisms metabolize glucose for energy, and so cellulose is a much more concentrated source of energy than is glucose. There is therefore great intrinsic value in cellulose, which is why plants evolved to produce lignin to protect it.

The polymer chains in lignin are highly irregular and arranged in networks around and between cellulose fibres. The chain links are ingeniously variable, able to form multiple chemical structures. When heated in fire, or subjected to industrial processing, lignin linkages break and re-form to make stronger ones. This remarkable self-healing capacity can be either destroyed or preserved when lignin is isolated. When self-healing is destroyed, unreactive technical lignin is produced. But lignin that retains its self-healing properties holds promise for making a new glue.

Until now, the marvellous structure and chemical reactivity of lignin has frustrated scientists' attempts to use it to make high-value products. Yang *et al*. describe a surprisingly simple, and yet chemically ingenious, strategy to remove lignin from wood while preserving its self-healing properties. The authors stir ground wood, organic solvent, a little acid catalyst and strategically chosen amounts of water and formaldehyde under heating. After cooling, the cellulose is filtered away for further use, and the lignin is readily processed into a water-dispersible powder, which is used to make a water-based glue.

And not just any glue, but a structural wood adhesive (Fig. 1): the type needed to make wood-based composites, such as plywood, that are used in structures (such as walls and floors) that support heavy loads in buildings. Structural-wood adhesives must pass rigorous performance tests to satisfy national and international building codes, and the authors report results indicating that their glue could meet structural certification requirements. In North America, most people's homes contain both structural and non-structural wood composites – the latter are used to make cabinets

From the archive

On the trail of organisms that cause human disease, and the inspirational life and work of Michael Faraday.

100 years ago

The bearings of zoology on human welfare — as illustrated by the relation of insects, protozoa, and helminthes to the spread ... of disease in man — have become increasingly evident ... At the time of the last meeting of the British Association in Liverpool (1896), insects were suspected of acting as transmitters of certain pathogenic organisms ... but these cases were few, and in no single instance had the life-cycle of the organism been worked out and the mode of its transmission ... ascertained.

From *Nature* 22 September 1923

150 years ago

[T]here is great need just now that some of the lessons to be learnt from Faraday's life should be insisted upon ... The simplicity of his heart, his candour, his ardent love of the truth, his fellow interest in all the successes, and ... admiration of all the discoveries of others, his natural modesty in regard to what he himself discovered, his noble soul — independent and bold — all these combined, gave an incomparable charm to the features of the illustrious physicist ... [T]he field of electro-magnetic science was already very large when Faraday first entered upon his public career ... [I]t was necessary that he should begin by getting rid of those parasitical ideas, which are so apt to cling to every scientific term, and to invest it with a luxuriant crop of connotative meanings flourishing at the expense of the meaning which the word was intended to denote. He therefore endeavoured to strip all such terms as "electric fluid," "current," and "attraction" of every meaning except that which is warranted by the phenomena themselves, and to invent new terms, such as " electrolysis," "electrode," and "dielectric" ... He thus undertook no less a task than the investigation of the facts, the ideas, and the scientific terms of electromagnetism, and the result was the remodelling of the whole according to an entirely new method.

From *Nature* 18 September 1873

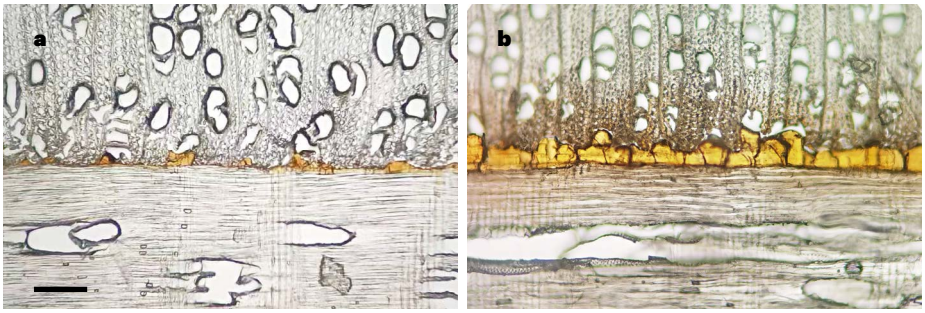

Figure 1 | Lignin glue at the interface between wood veneers in plywood. Yang *et al.*[1] report that lignin, a structural component of plants, can be extracted from wood and used as a glue to bond together wood veneers to form plywood. These optical microscope images show the glue at the interface between two veneers; the plywood in **a** was prepared at 100 °C, and that in **b** at 190 °C. The glue line is visible in amber, and is thicker in **b** because the glue flows more easily into voids in the wood at the higher temperature. Scale bar, about 100 micrometres.

and other indoor furnishings, for example. Both composite types are manufactured on large scales, and the market is diverse, highly competitive and begging for materials made using non-petrochemical adhesives. This is ideal for the commercialization of a new glue technology based on lignin.

The wood-composite and construction industries could have a big role in mitigating climate change, because great quantities of carbon can potentially be stored in materials used to build homes, offices and other buildings. Wood is currently the major feedstock for this strategy, along with increasing amounts of hemp, bamboo and other renewables. The United States is well placed to achieve net carbon storage in this way, because annual timber growth sustainably exceeds consumption (see go.nature.com/3sn7fct). But these industries will also need to reduce their overall energy consumption and adopt renewable energy sources — no small task. However, if a lignin waste stream can finally be used as a wood adhesive, then large-scale net-carbon storage becomes much more feasible for these industries.

"An important implication of this work is that it could enable the integration of plant-processing biorefineries."

An equally important implication of Yang and colleagues' work is that it could enable the integration of plant-processing biorefineries. For instance, a pulping unit that makes cellulose-based energy and chemicals could co-locate with a facility that produces plywood glue and another that manufactures plywood, at a site that has a large tree-processing infrastructure. Together, the three units would convert most of the tree biomass into high-value products, burning an efficiently minor waste stream for process energy. Such a fully integrated biorefinery would result in tremendous efficiencies, cost savings and reductions in carbon emissions compared with current facilities, as will be needed for a circular economy that minimizes waste and maximizes resource use.

One detail of Yang and colleagues' work is strikingly ironic: the process for making the glue requires formaldehyde, a petrochemical with a long history of regulation in the wood-products industry. The authors find that formaldehyde's ability to promote the isolation of self-healing lignin is unmatched by any other molecule — similar to the way in which formaldehyde is unrivalled as a component of currently available wood glues. However, formaldehyde can be toxic to humans. Some wood adhesives emit formaldehyde while in service in homes and offices — non-structural urea–formaldehyde (UF) resins are the best example.

Since the 1980s, government regulations have stimulated industry innovation such that formaldehyde emissions from non-structural wood glues have been steadily and substantially reduced (see go.nature.com/3ealdfe). Currently used formaldehyde-based adhesives emit at such low levels that emission-test failures are sometimes caused by the formaldehyde produced naturally by wood, rather than by the glue[2]. Yang *et al.* report that their glue meets or exceeds current emission standards — which it should, because formaldehyde becomes locked up in carbon–carbon bonds, rather than in water-sensitive nitrogen–carbon–nitrogen bonds, as it does in UF resins.

Should UF resins be dumped in favour of lignin glue? Probably yes. But this will take time, and even if UF resins are phased out, formaldehyde would still be needed to isolate lignin. But the benefits of using petrochemicals can outweigh the drawbacks. For instance, without the current use of a relatively small amount of petrochemical glues, the scale of timber waste would be heartbreaking — as it was before adhesives made it possible for

humans to use wood more effectively[3]. Now it seems that using formaldehyde for lignin isolation could provide much greater benefits for carbon sequestration, and on the scale needed to fight climate change. It is currently impossible to say for sure whether this will work – but I think it will.

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Cancer

Stem-cell clues to why vertebrae attract tumours

Geert Carmeliet

Tumour cells tend to migrate to the vertebrae rather than to long bones, but the mechanism underlying this has been unclear. It emerges that the stem cells from which vertebrae are derived make a factor that attracts tumour cells. **See p.602**

The spread of cancer cells to other organs, termed metastasis, is the main cause of cancer-related death. Bone is a common site for the spread of cancers originating in various organs, particularly the breast and prostate. This is because the bone microenvironment can both attract tumour cells and promote the growth of these cells to form bone-destroying metastases[1]. On page 602, Sun *et al.*[2] provide insight into the processes that underlie the spread of tumours to bone.

The metastasis of tumour cells to bone is not uniformly distributed throughout the skeleton; more tumours spread to the vertebrae in the spine than to the long bones of limbs[1]. This effect is thought to occur owing to the activity of previously unknown local factors that favour the survival and proliferation of tumour cells.

Irrespective of the skeletal site to which tumours spread, tumour cells in the bloodstream that enter the bone marrow interact with bone-forming cells called osteoblasts, both physically and through signalling molecules. This cooperation can increase the formation of osteoclasts – cells that break down bone – leading to harmful bone fractures and severe illness. A key question is whether bone-forming cells from different skeletal sites vary in their ability to attract tumour cells from the bloodstream and to mediate the formation of metastases. Sun and colleagues report that a type of skeletal stem cell (SSC) that can give rise to osteoblasts not only underpins the development and function of the vertebrae, but also mediates the spread of cancer to the spine.

A particular characteristic of bone is that there is not one general type of SSC, but rather a family of them, and some SSCs are found in distinct regions in long bones – for example, at sites known as the growth plate, endosteum, periosteum and bone marrow – and have overlapping but specific functions[3–5]. Given this finding, and the fact that the developmental origin of vertebrae is distinct from that of long bones[6], Sun *et al.* asked whether mouse SSCs for vertebrae differ from those for long bones.

The authors observed that the two SSC types had distinctive gene-expression profiles, and that the transcription factors ZIC1 and PAX1 were highly expressed in vertebral SSCs (Fig. 1). After verifying that ZIC1 and PAX1 could induce the expression of genes that are markers of vertebral SSCs, the authors developed a system that enabled them to specifically engineer this type of stem cell. Using this system, Sun and colleagues confirmed that ZIC1- and PAX1-expressing vertebral SSCs are true stem cells that have the capacity for *in vivo* self-renewal and the potential to differentiate into multiple cell lineages.

Sun *et al.* then used their engineered system in mice to investigate the developmental function of vertebral SSCs by manipulating the expression of the osteoblast-promoting (osteogenic) transcription factor osterix and of other regulators of osteoblast function. The affected mice exhibited changes in their vertebral bone mass, but the long bones were unaffected, indicating that vertebral SSCs are crucial for the production of osteoblasts and for enabling the formation of bone in the vertebrae.

Notably, the authors showed that cells of the vertebral-SSC lineage also contribute to bone problems that affect mainly the vertebrae, such as the formation of metastases. When breast cancer cells were injected into the bloodstreams of mice, more tumour cells were subsequently detected in the vertebrae than in the long bones, and the cancerous cells were found in close proximity to cells of the vertebral-SSC lineage. The preference of tumour cells to move towards the vertebrae was not caused by specific features of blood vessels, or by the rate of blood flow; instead, it depended on the presence of cells from the vertebral-SSC lineage.

Sun and colleagues confirmed this effect through experiments using bone organoids – 3D structures grown *in vitro* that resemble bone tissue – derived from vertebral SSCs. Specifically, they found that cells of this lineage produce high levels of the protein MFGE8, which stimulates the migration of tumour cells and is also likely to promote their growth.

The authors detected vertebral SSCs in human vertebrae, and they used bone

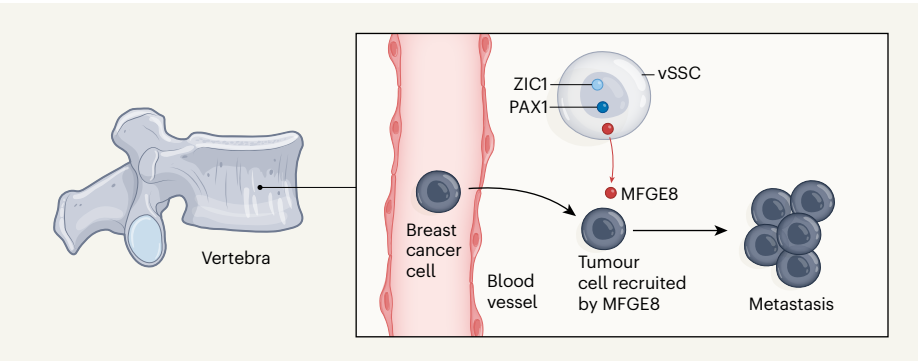

Figure 1 | A population of stem cells that attracts tumour cells to vertebrae. Sun *et al.*[2] examined the migration of breast cancer cells to the bones in mice. The authors identified a population of vertebral skeletal stem cells (vSSCs) that express the transcription factors ZIC1 and PAX1. Through their secretion of the protein MFGE8, these stem cells attract breast cancer cells from the bloodstream to form a secondary growth of tumour cells, called a metastasis.