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

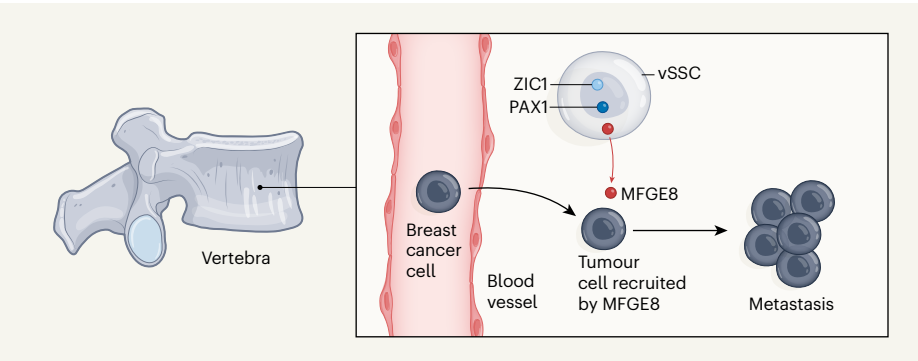

Figure 1 | A population of stem cells that attracts tumour cells to vertebrae. Sun *et al.*[2] examined the migration of breast cancer cells to the bones in mice. The authors identified a population of vertebral skeletal stem cells (vSSCs) that express the transcription factors ZIC1 and PAX1. Through 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.

organoids derived from human vertebral SSCs to show that the expression of MFGE8 in human vertebral-SSC-lineage cells mediates the formation of metastases. Thus, the identification of this previously unknown type of SSC broadens our understanding of the concept that a family of SSCs regulates bone characteristics in a regional manner, and that some features of vertebral SSCs mediate vertebra-related bone disease.

These insights raise several questions. The specific attributes of cells from the vertebral-SSC lineage are thought to drive the preference of tumours to spread to the vertebrae — in part through the secretion of MFGE8, which increases the migration of cancer cells to vertebrae. However, tumour cells also need to survive and proliferate in the bone environment[1], so a question that remains is whether cells of the vertebral-SSC lineage also regulate these aspects of metastasis.

The physiological function of vertebral-SSC-derived MFGE8 in the vertebrae is also yet to be determined. Furthermore, MFGE8 is produced by several types of skeletal cell, and its deletion throughout the body decreases bone mass in old mice[7,8]. Eliminating the expression of MFGE8 specifically in vertebral SSCs, rather than across the whole body, will enable determination of the physiological role of vertebral-SSC-derived MFGE8 in the vertebrae, and will provide insight into how MFGE8 is involved in attracting tumour cells from the bloodstream.

Ageing directly affects long-bone SSCs; the ageing process leads to a reduction in the capacity of these cells to generate osteoblasts, and to an increase in the production of factors that promote osteoclast activity, resulting in a loss of bone mass[9]. It will be interesting to investigate whether the mechanisms that impair the functions of vertebral SSCs are the same in older mice and in humans, and whether such mechanisms might account for the bone problems and vertebral fractures that occur in older people and after menopause[10].

"More tumours spread to the vertebrae in the spine than to the long bones of limbs."

Sun and colleagues' work enlarges the family of SSCs and raises the possibility that other types of SSC will be identified in the future. The authors report that deleting the gene that encodes osterix in ZIC1-expressing vertebral SSCs resulted in decreased bone mass in the vertebrae; however, some bone was nevertheless formed. That finding might indicate that another type of SSC is present in the vertebrae, which complements the ZIC1- and PAX1-expressing vertebral SSCs. Gaining insight into the specificities of SSCs in a range of skeletal regions could also aid efforts to develop treatments to combat the spread of tumours to the bones and to tackle vertebra-related bone disorders.

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