stable in recipient cells for only approximately 48 hours. Thus, the authors' method allows an evaluation of the initial changes that occur at metastatic sites through time, but is not suitable for long-term tracking.

Cancer cells can alter their local environment to promote tumour growth through processes such as driving blood-vessel formation to increase nutrient supply, or causing changes that protect the tumour against immune attack[6]. The rare cancer cells that successfully thrive at a distant site usually alter the microenvironment there to promote their growth by, for example, starving normal cells of metabolite molecules to increase nutrient availability[7], or preparing a microenvironment that promotes tumour growth[8,9]. Ombrato and colleagues used their tool to identify and isolate healthy cells for molecular analysis by methods that included RNA sequencing, to track changes that might promote the formation of the metastatic niche.

The authors showed that normal lung cells (of a type called an epithelial cell) that surrounded invading breast cancer cells belonged to a cell lineage known as alveolar type 2 (AT2) cells. Metastasizing cells benefited from this type of microenvironment, as demonstrated by Ombrato and colleagues' observation that cancer cells grown with lung epithelial cells *in vitro* had a high proliferation rate.

The AT2 cells that the authors identified in the vicinity of the invading cancer cells also had characteristics of a comparatively undifferentiated sort of lung cell — a stem cell[10–14]. In the lung, most AT2 cells are fully differentiated, with only a small subset behaving like stem cells[15]. Do these cancer cells prefer to locate near lung stem cells, or do they drive the recruitment of such cells to their vicinity? Alternatively, might the cancer cells drive neighbouring differentiated AT2 cells to take on a stem-cell-like fate?

To investigate these possibilities, Ombrato and colleagues studied cancer cells grown *in vitro* with AT2 cells. This revealed that the presence of the cancer cells boosted the capacity of AT2 cells to act as stem cells and to give rise to various types of differentiated lung cell, compared with AT2 cells grown in the absence of cancer cells.

Future *in vivo* studies combining Ombrato and colleagues' labelling approach with other methods for tracing the lineage of lung stem cells will undoubtedly help to resolve how metastatic breast cancer cells create a microenvironment that nurtures tumour cells in the lung. The observation that breast cancer cells form a metastatic niche near lung stem cells is reminiscent of a previous observation: when prostate cancer cells metastasize to the bone, they settle near stem cells in the bone marrow, which helps to provide an environment that supports tumour growth[16].

Ombrato and colleagues' method holds great promise for addressing why a given type of cancer cell preferentially migrates to a particular initial secondary site, such as the bone marrow or lung. This key question has not been fully answered. Using the authors' technique to study breast cancer cell lines that have distinct organ preferences for their secondary sites[17] should provide insight about the mechanisms underlying such preferences.

It will be important to determine whether the authors' findings in mice are relevant for human cancer. In samples of human lung tissue containing metastatic breast cancer cells, Ombrato *et al.* found that lung epithelial cells neighbouring the tumour expressed a higher level of a protein associated with proliferation than did lung epithelial cells located farther away from the site of tumour invasion. Analyses to understand how this type of dividing cell supports breast cancer growth are essential areas for future studies.

If migrating tumour cells could be prevented from lodging in distant organs, this would have a major positive clinical impact. Because cancer cells often have a high level of genomic alteration, focusing instead on their neighbouring cells, which are genetically more stable, might be an effective strategy for targeting a metastatic niche. The complexity of the microenvironment at such sites, in which components such as immune and non-immune cells affect the settlement of cancer cells, will need to be characterized in depth to test whether manipulation of such regions is a potential therapeutic strategy. Ombrato and colleagues' method provides a crucial way forward for such endeavours. ■

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ARTHRITIS

An immune-cell barrier protects joints

Inflammation and the repair of damaged tissues are regulated by immune cells called macrophages. The finding that they form a layer that shields mouse joints from damage has implications for the treatment of arthritis. SEE LETTER P.670

CHRISTOPHER D. BUCKLEY

Immune cells called macrophages commonly function as scavenger-like (phagocytic) cells that ingest and remove damaged cells. Culemann *et al.*[1] report on page 670 that the macrophages present in joints also fulfil an unexpectedly different role.

Macrophages derive from two main cellular lineages[2]. One lineage arises from bone-marrow-derived immune cells called monocytes. The other lineage is monocyte independent, and is derived from cells that disperse into the tissues during embryonic development[2]. The tissue-resident macrophages in this lineage have distinctive gene-expression profiles[3,4] that depend on the particular tissue in which they reside.

Rheumatoid arthritis is an immune-mediated disease associated with inflammation and the destruction of the cartilage and bone in joints, and macrophages have a key role in the initiation of this condition. However, little is known about the relative contribution of the two lineages of macrophages to the development and function of joints in health and disease. To add to the complexity, macrophages exist as various subsets, some of which are pro-inflammatory, whereas others are anti-inflammatory and aid tissue repair[5].

To study macrophages, the authors began by focusing on a protein called CX3CR1, which is expressed on monocytes and macrophages. The authors engineered CX3CR1-expressing

cells in mice to make a red fluorescent protein so that the cells could be tracked *in vivo*. These cells were monitored in knee joints using an approach called 3D light-sheet fluorescence microscopy, and the joint tissue was treated using a technique that enabled the authors to obtain 'optical clearance', which improves the visualization of internal structures[6].

Unexpectedly, the authors' observations revealed that CX3CR1-expressing macrophages exist as a layer of cells that forms a barrier, similar to a thin protective membrane, in the healthy joint (Fig. 1). This barrier forms as an outer layer of cells in the synovium, a region of the tissue that lines the joint. The barrier layer forms in a part of the synovium called the lining layer, and it physically separates the synovial fluid (which bathes the joint) from the sublining layers of the synovium. The CX3CR1-expressing barrier-forming macrophages are found adjacent to a layer of cells called fibroblasts in the lining layer.

The authors carried out RNA sequencing, including single-cell sequencing, to profile the barrier macrophages. These cells express genes typically associated with barrier formation in a type of non-immune cell called an epithelial cell. For example, the macrophage profile included genes that encode proteins associated with the formation of a structure called a tight junction that connects epithelial cells by forming a 'seal' between adjacent epithelial cells. This is surprising, because macrophages are usually thought of as having a signalling or scavenging role, rather than having a structural, barrier-like function.

Using a mouse model of arthritis in which macrophages could be tracked by engineering them to be fluorescent, the authors observed that the barrier layer was highly dynamic. When arthritis was induced, the layer underwent active remodelling that loosened the physical interactions between barrier macrophages and lining-layer fibroblasts. Like other types of tissue-resident macrophage, the barrier macrophages can ingest and remove inflammatory immune cells called neutrophils that accumulate and die in the synovial fluid in arthritis.

When the authors induced arthritis in mice at the same time as they disrupted the barrier-forming layer of macrophages through genetic or pharmacological manipulation, arthritis was more severe than in animals in which the layer was intact. It would be interesting to test whether transferring barrier macrophages directly into mouse joints could suppress arthritis.

To explore the origin of the barrier-forming, CX3CR1-expressing macrophages, the authors used intricate fate-mapping experiments, which revealed that these cells are not derived from monocytes. They also found that monocytes did not give rise to the other type of macrophage that resides in the joint, termed an interstitial synovial macrophage, which populates the sublining layer. The authors' data are consistent with a model in which interstitial macrophages give rise to barrier macrophages.

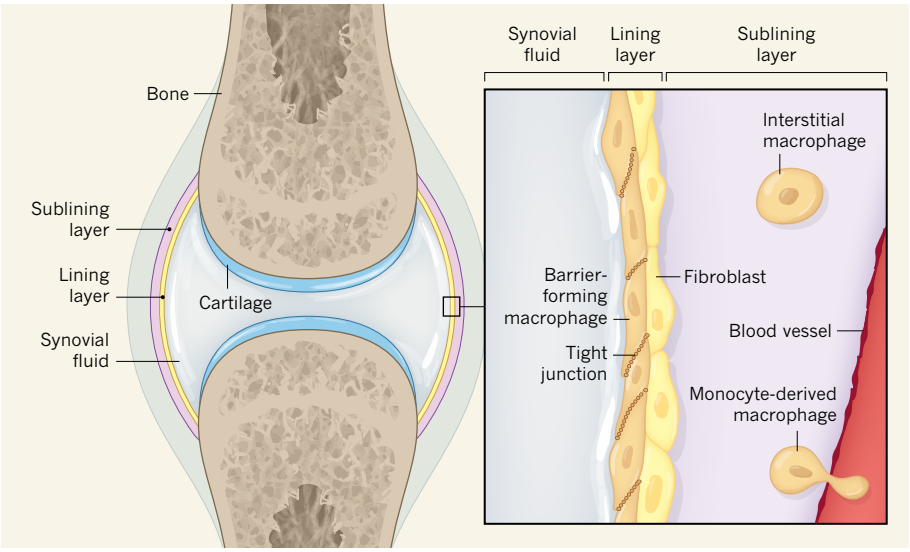

Figure 1 | Barrier macrophages in the joint. Culemann *et al.*[1] studied immune cells called macrophages in mouse and human joints. Joints are surrounded by a tissue called the synovium, which is formed from layers of cells called the lining and the sublining layers. The authors discovered that certain macrophages form a cell layer that protects joints from the inflammatory immune-cell attacks on bone and cartilage that are associated with arthritis. This barrier is formed in the lining layer, adjacent to a layer of cells called fibroblasts. The barrier-forming macrophages express proteins associated with a type of barrier-forming cell called an epithelial cell, and these proteins form structures called tight junctions that 'seal' cells together. Barrier-forming macrophages arise from a type of macrophage called an interstitial macrophage, which resides in the sublining layer. By contrast, non-resident macrophages enter the joint from blood vessels. These cells, which can drive inflammation, arise from immune cells called monocytes.

RNA-sequencing experiments revealed that interstitial macrophages can be divided into two groups. One group expresses the gene *Retnla*, whereas the other has a high level of expression of the genes that encode the proteins MHC class II and aquaporin. Cells of the latter group divide and differentiate to form either barrier macrophages, or interstitial macrophages that express *Retnla*.

To analyse the macrophage subsets that arise as arthritis develops, compared with those present in an uninflamed joint, the authors carried out further single-cell RNA sequencing. As expected from previous work[7], monocyte-derived macrophages that produce pro-inflammatory molecules accumulated in the arthritic joint. They are recruited into the joint from the bloodstream, exiting blood vessels to enter the sublining layer. During the influx of these pro-inflammatory macrophages, the barrier macrophages maintained their anti-inflammatory role, expressing the proteins needed for them to remove dead neutrophils from the joint.

When the authors compared their single-cell RNA data from mice with similar data sets[8] available from an analysis of the joints of people with rheumatoid arthritis, the gene-expression profiles of the macrophage subsets matched up between the two species. This suggests that cells similar to the barrier and interstitial macrophages in mice might also exist in humans, and thus be relevant to human disease.

The authors found that barrier macrophages were almost totally absent in synovial samples from people with active rheumatoid arthritis, whereas they made up 10% of the macrophage population in samples from people who have osteoarthritis, a type of arthritis that is not associated with inflammation. It would be interesting to learn whether the population of barrier macrophages is restored in people whose rheumatoid arthritis is being successfully treated and is in remission.

Culemann and colleagues' work adds to studies[3,4,9] showing that macrophages are exquisitely adapted to the functions they perform in the tissues in which they reside. Barrier macrophages join a growing list of types of macrophage that shield tissues from damage caused by infection, inflammation or cancer. Tissue-resident macrophages can prevent neutrophil-mediated inflammatory damage by physically shielding damaged tissue from neutrophils[10]. Furthermore, in large body cavities, such as those surrounding the gut, heart and lungs, specialized macrophages have been described that are thought to repair mechanical damage[3,9]. These findings also complement the discovery of distinct subsets of fibroblasts, located in the sublining or lining regions of the joint, which, respectively, drive either inflammation or bone damage in arthritis[11]. The challenge that lies ahead will be to develop ways of specifically targeting subsets of macrophages and fibroblasts with the ultimate goal of developing new treatments for people with arthritis. ■

50 Years Ago

Medical geography could soon benefit considerably from computer graphics … Medical geography is concerned with variations in the incidence of disease in different areas and the link with possible causes connected with elements of the physical, biological and sociocultural environment. As such it is a topic in which maps should be valuable, but they are often of little use because of the time taken for such lengthy and repetitive processes as the calculation and statistical testing of attack rates, fatality rates, standardized mortality ratios and other disease indices. And it takes a long time to represent these indices in cartographic form. Computer graphics — the construction of maps and diagrams using the electronic computer — could have considerable potential in medical geography. They may, by the speed, efficiency and reliability of processing and mapping medical data, lead to a more effective use of maps.

From *Nature* 30 August 1969

100 Years Ago

The Medical Research Committee has issued a report … on the influence of alcohol on manual work and neuromuscular co-ordination. Accuracy and speed in typewriting and in using an adding machine, and accuracy in hitting spots on a target, were used as tests, and both pure alcohol and alcohol in the form of wine and spirit were employed. There was no distinct difference between the two forms of alcohol, and when very dilute (5 per cent.) the effect was about three-fourths as great as when taken strong (37–40 per cent.) for the same amount of alcohol … The degree of effect depended largely on whether the alcohol was taken on an empty stomach or with food; on an average it was twice as toxic under the former condition.

From *Nature* 28 August 1919

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CONDENSED-MATTER PHYSICS

Superconductivity seen in a nickel oxide

Magnetism alone was thought to be responsible for superconductivity in copper oxides. The finding of superconductivity in a non-magnetic compound that is structurally similar to these copper oxides challenges this view. SEE LETTER P.624

GEORGE A. SAWATZKY

In 1986, scientists unexpectedly discovered that a lanthanum barium copper oxide, $La_{1.85}Ba_{0.15}CuO_4$, becomes a superconductor (has zero electrical resistance) below a relatively high temperature[1] of 35 kelvin. This result triggered one of the most intense experimental and theoretical research efforts in condensed-matter physics. Soon afterwards, many other copper oxides (cuprates) were found to superconduct at temperatures[2] of up to 133.5 K. However, after more than 30 years, there is no consensus regarding the underlying mechanism of cuprate superconductivity. On page 624, Li *et al.*[3] report that a neodymium strontium nickel oxide, $Nd_{0.8}Sr_{0.2}NiO_2$, superconducts below 9–15 K. This material has a similar crystal structure to that of the cuprate superconductors, suggesting that the authors' discovery could lead to a better understanding of superconductivity in these systems.

Superconductivity can occur in a metallic material if the usual repulsive interaction between electrons turns into an attractive one. In this scenario, the response of surrounding atoms to the charge and spin (magnetic moment) of electrons indirectly leads to electron pairing. At a low enough temperature, these paired electrons condense to form a superfluid (a state of matter that flows without friction), which exhibits zero electrical resistance[4]. The key to understanding superconductivity in a given material is to identify the mechanism that provides the 'pairing glue'.

In the conventional mechanism, the spatial displacement of atoms close to an electron forms an attractive region for another electron[4]. An analogy is that of two heavy balls on a spring mattress, whereby the indentation in the mattress made by one of the balls produces an attractive region for the other ball. However, some theoretical work has suggested that this effect is too small to account for the high-temperature superconductivity of the cuprates.

Researchers have therefore considered that the spins of moving electrons might cause deviations in the magnetic order (the ordered pattern of atomic spins) in the cuprates. With respect to the mattress analogy, these deviations represent mattress indentations, and the strong interactions between the spins of neighbouring Cu^{2+} ions represent the mattress springs. To understand how this mechanism works, consider the cuprate superconductor $La_{1.85}Ba_{0.15}CuO_4$, which is obtained from the compound La_2CuO_4 by replacing some lanthanum atoms with barium.

In La_2CuO_4, the electrons of a particular Cu^{2+} ion are prevented from moving by their strong repulsion to the electrons of surrounding Cu^{2+} ions. As a result, the material is an electrical insulator[5]. Each Cu^{2+} ion has an odd number of electrons and a net spin of 1/2. The ions have strong antiferromagnetic order, which means that the spins of neighbouring ions point in opposite directions.

When lanthanum in La_2CuO_4 is partially replaced with barium, electron vacancies called holes are introduced into the system in a process known as doping. These holes migrate to the planes of CuO_2 in the material. If their density is low enough, they act as freely moving charge carriers, resulting in metallic behaviour. The combination of a Cu^{2+} ion and a doped hole has an even number of electrons and a net spin of 0, which causes a severe disturbance in the spin directions of surrounding