sides would sooner see Solomon split the baby — that is, suffer a devastating deadlock — than concede. Nevertheless, more-general forms of information gerrymandering might be possible, even in these cases. For example, people are more likely to vote in elections that they believe to be close contests[6]. Network structures that skew perceptions of others' voting intentions in a way that influences voter turnout by a particular group could be construed as information gerrymandering. The same could be said of network structures that drive asymmetric patterns of social contagion.

The implications of Stewart and colleagues' work are alarming. In the past, information was disseminated by a small number of official sources such as newspapers and television stations, or through real-world social networks that emerged largely from distributed processes involving individual interpersonal dynamics. This is no longer the case, because social-network websites deploy technologies that restructure social connections by design. These online social networks are highly dynamic systems that change as a result of numerous feedbacks between people and machines. Algorithms suggest connections; people respond; and the algorithms adapt to the responses. Together, these interactions and processes alter what information people see and how they view the world. In addition, micro-targeted political advertising offers a surreptitious and potent tool for information gerrymandering. Alternatively, information gerrymandering might arise without conscious intent, but simply as an unintended consequence of machine-learning algorithms that are trained to optimize user experience.

At present, online social networks are not subject to substantive regulations or transparency requirements. Previous communication technologies that have had the potential to interfere with the democratic process — such as radio and television — have been subjected to legislative oversight[7]. We suspect that the social-media ecosystem is overdue for similar treatment. ■

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IMMUNOLOGY

Immune-cell function under pressure

Immune cells called monocytes enter the lung during infection. Whether they help to launch a defence response is affected by the pressure encountered there, which is sensed by an ion channel called PIEZO1. SEE ARTICLE P.69

SARAH R. WALMSLEY

An effective immune response to general signs of infection, regulated by the branch of the immune system called innate immunity, is essential for the removal of unwanted bacteria. Such a response should then end when the infection is over — dampening and blocking any unwanted inflammatory response. The processes that determine whether inflammation is effective or dysfunctional are of considerable therapeutic interest, given the lack of available strategies to target harmful inflammation while preserving beneficial host defences. Efforts to understand how immune cells respond to inflammation have, in turn, focused attention on immune regulatory processes. These include processes involved in sensing the damage associated with infection[1], as well as those needed to recognize other infection-related changes, such as alterations in nutrient[2] or oxygen levels[3,4]. Solis *et al.*[5] reveal on page 69 that mechanical cues generated in the mouse lung are sensed by immune cells and are crucial regulators of an immune response.

The immune system's myeloid cells — a group that includes macrophages and monocytes — are exposed to a range of physical forces, for example those encountered when leaving blood vessels to enter tissues[6]. Cycles of mechanical force occur in organs such as the lung, in which tissues are compressed during breathing[7]. These forces are themselves subject to change in disease states; for example, when tissue swells during an inflammatory response. Solis and colleagues report that macrophages and monocytes can respond to mechanical cues that are perceived through a mechanosensory ion channel called PIEZO1 that is located on their cell surface.

To understand whether the exposure of myeloid cells to mechanical forces could directly regulate immune-cell function, the authors generated mice that lacked PIEZO1 in myeloid cells. Using an *in vitro* system, the

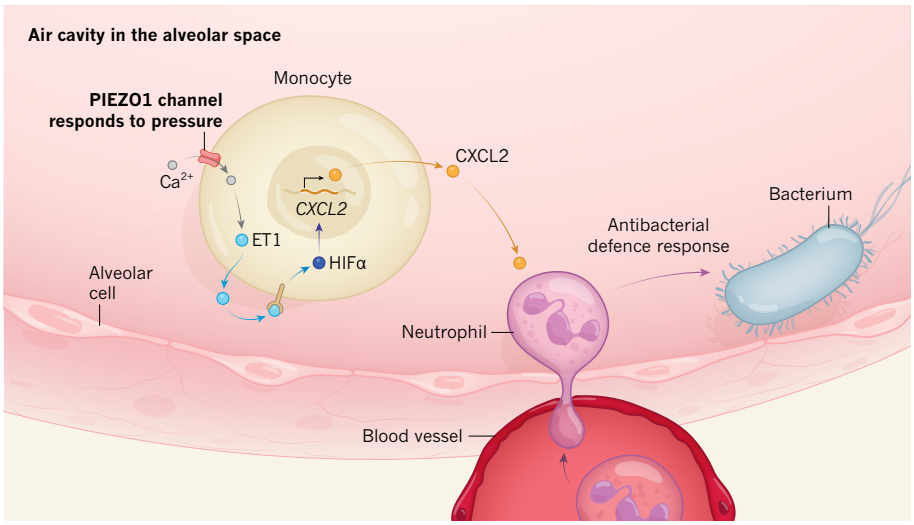

Figure 1 | Immune cells in the lung respond to pressure by triggering a defence response. By studying mouse immune cells grown *in vitro* and mouse models of bacterial infection of the lung, Solis *et al.*[5] investigated how immune cells called monocytes respond to the cycles of pressure that occur during breathing. They focused on structures in the lung called alveoli, which are the 'air sacs' of this organ. The authors report that pressure activates a mechanosensory receptor protein called PIEZO1 on monocytes, triggering an influx of calcium ions (Ca^{2+}). This leads to the expression of the hormone endothelin 1 (ET1), which is secreted from the cell. When it binds to its receptor, this stimulates a signalling pathway that stabilizes the protein HIFα, which drives the expression of pro-inflammatory genes. One such gene encodes the protein CXCL2, which is secreted from the cell. CXCL2 attracts a type of immune cell called a neutrophil, which enters the lung from the bloodstream, whereupon it can target bacteria that are present.

authors subjected immune cells to cycles of pressure change, mimicking those encountered in the lung, called cyclical hydrostatic pressure. The authors compared wild-type and PIEZO1-deficient macrophages and monocytes, which revealed that cyclical hydrostatic pressure induces a pro-inflammatory gene-expression profile in wild-type cells that depends on PIEZO1. This expression profile included genes that are controlled by the transcription-factor protein HIF1α, a key regulator of gene expression that is needed for myeloid cells to function and survive[8–10]. Interestingly, this pro-inflammatory gene-expression response was unaffected by the magnitude of the pressure encountered.

To understand the mechanisms driving this transcriptional response, the authors studied macrophages that were deficient in HIF1α. They found that the cells were unable to mount a pro-inflammatory gene-expression response to cyclical hydrostatic pressure. The authors reveal that subjecting wild-type cells to this type of pressure in the *in vitro* system drives an influx of calcium ions into cells through the PIEZO1 channel, which results in accumulation of HIF1α (Fig. 1). This PIEZO1-mediated boost to HIF1α required the production of the hormone endothelin 1, which acts in a signalling pathway that stabilizes HIF1α in cells[11,12]. Endothelin 1 is secreted by cells and acts by binding to its receptor either on the cell that secreted it or on a neighbouring cell.

To test the role of PIEZO1-mediated signalling in host defences, Solis and colleagues used a mouse model of pneumonia in which infection is caused by the bacterium *Pseudomonas aeruginosa*. Compared with wild-type mice, animals that were engineered to lack PIEZO1 in myeloid cells had fewer immune cells called neutrophils in the lung tissues, and lower levels of pro-inflammatory immune-signalling molecules in the lungs, such as endothelin 1. They also had lower levels of the protein CXCL2, which attracts neutrophils. Such mice had higher levels of bacteria in their lungs and greater bacterial spread to the liver compared with wild-type mice.

The authors report that production of endothelin 1 was not affected if PIEZO1 was depleted in mouse macrophages found in a lung structure called the alveolus, or if the ion channel was depleted in dendritic cells, which are another type of lung immune cell. However, depleting monocytes caused a reduction in the levels of endothelin 1, implicating the cells as a source of this hormone. The authors confirmed that PIEZO1-dependent production of endothelin 1 has a key role in defences against infection, by showing that administering endothelin 1 to mice lacking PIEZO1 in myeloid cells reduced the burden of unwanted bacteria, when compared with the bacterial burden in such animals that did not receive endothelin 1. Solis and colleagues' work is consistent with a model in which PIEZO1-mediated mechanosensation by monocytes in the lung activates these cells to produce endothelin 1, driving a rise in the level of HIF1α and a pro-inflammatory gene-expression profile. In turn, that results in the recruitment of neutrophils, which help to get rid of unwanted bacteria.

These observations raise key questions regarding the broader relevance of PIEZO1 signalling in other diseases associated with altered lung mechanics, such as pulmonary fibrosis. This condition is characterized by high levels of immune cells in the lungs, a reduction in lung elasticity and restricted airflow. Solis and colleagues report that mice lacking PIEZO1 in myeloid cells are protected from lung damage in a mouse model of pulmonary fibrosis, which suggests that PIEZO1-regulated immune-cell function might have a role in human disease. This should be an area of focus as these studies continue.

Understanding how signals are integrated to mediate an effective immune response will require a greater depth of understanding than we have now. This is relevant in this case because immune cells move between different compartments in the lung, and are thus exposed to a range of environmental cues. Although PIEZO1 can promote a pro-inflammatory response that boosts the removal of unwanted bacteria, loss of this ion channel can also be beneficial, given that it can protect from the damaging inflammation associated with the mouse model of pulmonary fibrosis. Dissecting the regulatory steps that maintain a balanced, effective immune response will be necessary for exploring therapeutic avenues to target mechanosensory pathways during lung inflammation. ■

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EARTH SCIENCE

Similar starts for small and large earthquakes

A long-standing question in seismology is whether small and large earthquakes have similar or different onsets. An analysis of earthquakes around Japan shows that, in some cases, these onsets are almost identical. SEE LETTER P.112

RACHEL E. ABERCROMBIE

When can we know how large an earthquake will be? Is the magnitude of an earthquake controlled by the conditions and dynamics at the start of its growth? If so, measurements of the initial seismic waves from an earthquake, and even of the area in which it will occur, could enable early warnings of ground shaking. If not, then the chances of such short-term prediction are low. On page 112, Ide[1] compares the onsets of thousands of large earthquakes around Japan with those of nearby small ones. He finds that the onsets of about 20% of large earthquakes are indistinguishable from those of closely located small ones, within the frequency range of the seismic waves that he analysed.

Earthquakes often begin with a short phase of small-amplitude waves only, before growing to the final-sized event[2,3]. One mechanism that could explain this observation is a cascading failure, in which changes in stress from one randomly failing patch of geological fault cause other patches to fail — like toppling dominoes. In this case, the magnitude of an earthquake is controlled by the dynamic conditions as the event grows, and is impossible to predict until the quake slows or stops.

An alternative possibility involves slow slip — the relative movement of the rocks on either side of a fault. This slip, which is undetectable by seismometers, could gradually accelerate in a limited region of the fault before attaining a critical speed and breaking out to reach the final quake size. If correct, the earthquake magnitude might be determined by the size of the region of preceding slow slip