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. ■

Sarah R. Walmsley *is at the Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh EH16 4TJ, UK.*
e-mail: sarah.walmsley@ed.ac.uk

1. Huang, C. & Niethammer, P. *Immunity* **48**, 1006–1013 (2018).
2. O'Neill, L. A. J. & Hardie, D. G. *Nature* **493**, 346–355 (2013).
3. Sadiku, P. & Walmsley, S. R. *EMBO Rep.* **20**, e47388 (2019).
4. Taylor, C. T. & Colgan, S. P. *Nature Rev. Immunol.* **17**, 774–785 (2017).
5. Solis, A. G. *et al. Nature* **573**, 69–74 (2019).
6. Begandt, D., Thome, S., Sperandio, M. & Walzog, B. *J. Leukoc. Biol.* **102**, 699–709 (2017).
7. Mead, J. & Whittenberger, J. L. *J. Appl. Physiol.* **5**, 779–796 (1953).
8. Kaelin, W. G. Jr & Ratcliffe, P. J. *Mol. Cell* **30**, 393–402 (2008).
9. Lin, N. & Simon, M. C. *J. Clin. Invest.* **126**, 3661–3671 (2016).
10. Palazon, A., Goldrath, A. W., Nizet, V. & Johnson, R. S. *Immunity* **41**, 518–528 (2014).
11. Liu, Y. V. *et al. J. Biol. Chem.* **282**, 37064–37073 (2007).
12. Li, M. *et al. FEBS Lett.* **586**, 3888–3893 (2012).

This article was published online on 21 August 2019.

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

CHRIS MCGRATH/GETTY

Figure 1 | Impact of the 2011 Tohoku-Oki earthquake. On 11 March 2011, the strongest recorded earthquake in Japan's history triggered a tsunami that caused devastating damage. Ide[1] finds that large earthquakes can have almost identical onsets to those of small ones — with implications for predicting the final size of an earthquake.

or by the characteristics of the initial waves; and if these properties could be observed and understood, short-term prediction might be possible.

Some studies of seismometer records have found that earthquake magnitude is independent of the first few hundredths of a second[4] or longer[3]. However, these analyses were limited to only a few earthquakes. Other studies[5,6] have suggested a dependence of the final quake size on the onset. But these analyses involved indirect parameterizations of the data, and might not accurately account for the energy loss of seismic waves as they travel through Earth[7].

Ide compared the onsets of closely located earthquakes of different magnitudes to determine whether these onsets provide any indication of final quake size. He carried out a comprehensive analysis of all of the large earthquakes that were recorded in sufficient detail, between June 2002 and April 2018 along about 1,100 kilometres of the Japan Trench — a subduction zone, in which the Pacific Plate beneath the Pacific Ocean is being pushed under the Okhotsk Plate beneath Japan. He followed a procedure that has been used to identify phenomena known as repeating earthquakes[8]. These are similarly sized quakes whose seismometer records are so alike that the events must involve repeated, similar movement of the same patches of fault[8].

Instead of searching for similarly sized events, Ide started with 1,654 large earthquakes (of magnitude greater than 4.5) and compared them with all of the known small events (of magnitude less than 4) that are positioned closely enough (within about 100 metres) for their locations to be indistinguishable. He then calculated the similarity between the first 0.2 seconds of the seismometer records of these quakes.

Ide discovered 390 pairs of large and small earthquakes that have highly similar beginnings, with the onsets of 200 of the large events being indistinguishable from those of approximately co-located small events. He interpreted this finding to indicate that the onsets of large earthquakes can be identical to those of small ones, and therefore that the initial conditions and dynamics of a quake do not determine its magnitude.

By separating the earthquakes into subduction-type events — similar to the 2011 Tohoku-Oki earthquake (Fig. 1) — and other types, Ide discovered that the subduction-type earthquakes are more likely than the others to have paired events. He also found that the subduction-type pairings can be separated by more than ten years, whereas those of the other types are limited to small earthquakes occurring close in time to the large event.

The author interpreted these results using a model in which an earthquake fault consists of patches that have a range of sizes and relatively constant rupture characteristics. Slip of one such patch might trigger slip of a larger neighbouring patch, and so on. This picture is consistent with numerical models that have been proposed to explain repeating earthquakes[9]. The similarity of onsets over extended time periods implies that a long-term characteristic structure is present and able to repeatedly host large and small quakes.

By considering co-located earthquakes, in which the seismic waves from both small and large events take the same paths to measuring stations, Ide eliminated bias from waves travelling different paths through Earth[3,4]. His conclusion that the onset of an earthquake does not control its final size agrees with detailed observations of well-recorded quakes on the San Andreas Fault in Parkfield, California[10]. It is also consistent with global statistical compilations of large earthquakes[5,7,11] that found that all quakes grow at approximately the same rate and start to differ only when the rupture shows signs of slowing.

Most earthquakes around Japan occur offshore or deep underground, and so are not close to seismometers, limiting the spatial coverage and frequency range of recording. Ide's analysis focuses on high-frequency waves (of 1 hertz and above). It therefore misses any onset differences at the lower frequencies at which most of the energy is released by large quakes. It would also miss any preceding slow slip such as that observed in laboratory experiments and numerical models[12] — reliable, consistent observations of this slow slip before actual earthquakes remain elusive.

Another issue is that, even though Ide aimed to compare large and small earthquakes, about 60% have a magnitude difference of less than 1.5, similar to the variation seen in repeating-earthquake sequences[8]. Only about one-eighth of the paired events have a magnitude difference of more than 2.

For now, earthquake-prone populations must rely on earthquake early-warning systems, which have been long established in Asia and have been introduced in the past few years in California. These warning systems involve estimating earthquake magnitude using near-source seismometers, and sending this information to vulnerable populations ahead of the more slowly travelling, damaging seismic waves[13]. Ide's results are a key step towards a better understanding of earthquake initiation — knowledge that could improve the speed and accuracy of these warnings. ■

Rachel E. Abercrombie *is in the Department of Earth & Environment, Boston University, Boston, Massachusetts 02215, USA.*
e-mail: rea@bu.edu

1. Ide, S. *Nature* **573**, 112–116 (2019).
2. Ellsworth, W. L. & Beroza, G. C. *Science* **268**, 851–855 (1995).
3. Abercrombie, R. & Mori, J. *Bull. Seism. Soc. Am.* **84**, 725–734 (1994).
4. Mori, J. & Kanamori, H. *Geophys. Res. Lett.* **23**, 2437–2440 (1996).
5. Olson, E. L. & Allen, R. M. *Nature* **438**, 212–215 (2005).
6. Colombelli, S., Zollo, A., Festa, G. & Picozzi, M. *Nature Commun.* **5**, 3958 (2014).
7. Meier, M.-A., Ampuero, J. P. & Heaton, T. H. *Science* **357**, 1277–1281 (2017).
8. Uchida, N. & Bürgmann, R. *Annu. Rev. Earth Planet. Sci.* **47**, 305–332 (2019).
9. Noda, H., Nakatani, M. & Hori, T. *J. Geophys. Res. Solid Earth* **118**, 2924–2952 (2013).
10. Uchide, T. & Ide, S. *J. Geophys. Res. Solid Earth* **115**, B11302 (2010).
11. Noda, S. & Ellsworth, W. L. *Geophys. Res. Lett.* **43**, 9053–9060 (2016).
12. Kaneko, Y., Nielsen, S. B. & Carpenter, B. M. *J. Geophys. Res. Solid Earth* **121**, 6071–6091 (2016).
13. Allen, R. M. & Melgar, D. *Annu. Rev. Earth Planet. Sci.* **47**, 361–388 (2019).