used by LIGO. Suspended interferometers measure the phase of the output field of light waves, which is affected by both amplitude and phase fluctuations of the input vacuum field. This correlation is called the ponderomotive effect[2]. The detection response of the instrument is frequency dependent, and the effects of the amplitude fluctuations are more evident in the low-frequency realm of the detection band, whereas the phase fluctuations are more evident at high frequencies.

Light that has correlations between the uncertainties of its amplitude and phase is said to be 'squeezed'. The Heisenberg principle still holds for squeezed light states, but when one of the uncertainties is reduced, the other is increased. Squeezed light can be used in experiments to reduce the uncertainty of one of the correlated parameters. A special case of squeezed light, known as the squeezed vacuum, forms when the average amplitude of the light is zero.

Phase-squeezed light, in which the uncertainty associated with the phase is squeezed, has been used to reduce shot noise for both LIGO[3] and Virgo, the gravitational-wave detector located in Cascina, Italy[4]. And the ponderomotive effect has previously been demonstrated using the mechanical motion of pico- to microgram-scale mirrors in laboratory experiments[5,6]. Yu *et al.* now confirm that the ponderomotive effect occurs in the optical cavities of the LIGO interferometer, and have investigated whether it can be used in combination with squeezed-vacuum states to reduce quantum noise below the SQL in measurements of mirror position in the cavities.

The authors measured the noise in the LIGO interferometer under two sets of experimental conditions: one in which squeezed-vacuum states were injected into the output port of the interferometer, and another in which squeezed-vacuum states were not injected. They then plotted sensitivity curves for the data, which chart the noise level in the detector and define the minimum gravitational signal that can be detected as a function of the signal's frequency. This revealed that, once classical (non-quantum) noise had been subtracted from their data, the uncertainties in the phases of the laser beam and in the positions of the mirrors produce a combined quantum noise below the SQL. Yu and colleagues have therefore demonstrated two fundamental points: that quantum fluctuations of light exert a measurable force on macroscopic objects (the 40-kg mirrors); and that the quantum noise corresponding to these disturbances can be reduced to below the SQL.

One of the main difficulties for these kinds of measurement is thermal fluctuations — which can drive mirror motion and are one of the main sources of noise for gravitational-wave detectors. Cryogenic conditions have therefore been needed in some previously reported experiments[7,8] to reduce quantum noise to less than the SQL. Impressively, Yu and co-workers' measurements were made at room temperature.

Yu *et al.* are the first to have proved experimentally that a quantum non-demolition technique — a method in which a measurement of a quantum system is performed repeatedly without perturbing it[9] — works in gravitational-wave detectors. At present, such detectors use phase-squeezed vacuum states to reduce shot noise, without considering the correlations that are introduced by the interferometer mirrors. This approach improves sensitivity only for gravitational signals in which the frequency is higher than 100 hertz, up to the limit of the detection band[6]. By contrast, Yu and colleagues' technique potentially enables broadband detection improvement. However, further work will be needed to reduce the classical noise in the interferometer.

Once better sensitivity has been developed, more gravitational waves could be detected than is possible at present. Future work in noise suppression will therefore take us towards an exciting era of sub-SQL performance of gravitational-wave detectors.

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Tumour biology

A 'safety net' causes cancer cells to migrate and grow

Emma Nolan & Ilaria Malanchi

Immune cells called neutrophils can support the spread of cancer. How neutrophils aid this process now comes into focus through insights into the function of structures called neutrophil extracellular traps. **See p.133**

A neutrophil is a type of immune cell that provides the body with one of its first lines of defence against infection. However, in many contexts, neutrophils also have the ability to promote metastasis — the migration of cancer cells from their primary site and their growth in other locations in the body. On page 133, Yang *et al.*[1] shed light on how neutrophils aid this deadly process.

A key feature of neutrophils is their ability to extrude a structure called a neutrophil extracellular trap (NET) into their surroundings (Fig. 1). This consists of a web of DNA coated in enzymes toxic to microorganisms, and it can trap and kill invading microbes. But in the lungs, NETs are induced by inflammation, and their tumour-boosting activity has been linked to NET-associated enzymes[2]. A growing body of evidence indicates that NETs mediate the development and enhancement of the invasive properties of cancer cells[3], but how they boost metastasis has remained largely unknown. Moreover, a mechanism that enables cancer cells to sense NETs has not been reported previously. Yang *et al.* now provide much-needed insight into the tumour-promoting effects of these traps.

The authors began by assessing NETs in primary and metastatic tumours from 544 people with breast cancer. NETs were scarce at primary-tumour sites, but were abundant in the liver — a common site of breast cancer spread. Importantly, the authors found an association between higher levels of NET DNA in the blood of people with early-stage breast cancer and subsequent metastasis of the cancer to the liver. This indicates that monitoring NET DNA in blood samples might be a way of assessing disease prognosis.

To investigate the relationship between NETs and cancer cells *in vivo*, the authors transplanted breast cancer cells of human or mouse origin into mice, and analysed metastatic tumour cells. They found that NETs accumulated in the liver in both mouse models tested. The finding is consistent with the results of the authors' analysis of tumours from people with cancer.

Yang *et al.* report that, in their mouse models, NETs were induced in the liver

before metastatic cells could be detected there. The authors show that the efficiency with which cancer cells metastasized to the liver depended on NETs, because metastasis in mice was substantially impaired on removal of NETs, either by means of the DNA-degrading enzyme DNase I or if the animals were genetically engineered to lack an enzyme required for NET formation[4].

Previous work[5] has led to the proposal that NET-dependent metastasis to the liver occurs through an indirect mechanism by the physical trapping of 'passer-by' cancer cells by NETs. Yang and colleagues showed that NET DNA directly stimulated the migration and adhesion of human breast cancer cells when tested *in vitro*.

The authors next sought to discover how this migratory behaviour is induced. By adding a tag to NET DNA and using it as bait with which to capture and identify proteins with which it interacts, they found a receptor called CCDC25 that could bind to NET DNA. It is present on the surface of cancer cells, and Yang and colleagues report that CCDC25 could bind to NET DNA with high specificity and affinity, enabling 'NET sensing' by cancer cells. Impressively, the authors identified the specific extracellular portion of CCDC25 that binds to NET DNA.

The authors confirmed that NET-mediated stimulation of cancer-cell migration is driven by CCDC25 by showing that depleting it from human breast cancer cells cultured *in vitro*, or from samples of patients' primary breast-tumour cells, drastically reduced migration of the cancer cells when tested *in vitro*. Compared with the case for mice in which CCDC25 was still present, eliminating CCDC25 from the surface of cancer cells in mice significantly lessened the development of metastasis to the liver and decreased metastasis to the lungs after inflammation-inducing treatment with the molecule lipopolysaccharide (LPS). The role of LPS in triggering lung metastasis associated with NETs was previously reported[2]. Yang *et al*. observed similar reductions in metastasis to the lung on LPS treatment in their experiments if they used animals obtained by crossing mice lacking CCDC25 with mice that model spontaneously forming breast cancer, called MMTV-PyMT mice. Interestingly, the role of the interaction between CCDC25 and NET DNA in supporting metastasis in the lungs might occur only in the context of infection, whereas its effect on liver metastasis might occur spontaneously.

Finally, Yang and colleagues reveal how tumour cells profit from this interaction with NETs. Using CCDC25 as 'bait' in a biochemical technique to fish out CCDC25-interacting proteins in cancer cells, they identified one such protein — integrin-linked kinase (ILK), an enzyme that regulates processes such as cellular migration and proliferation[6]. When ILK was removed or its downstream signalling partner, the protein β-parvin, was disabled, cancer-cell growth and motility *in vitro* were substantially impaired and, in mice, metastasis to the liver was reduced. Together, the authors' results indicate that the binding of NET DNA to CCDC25 enhances aggressive cancer-cell behaviour by activating an ILK-mediated signalling cascade.

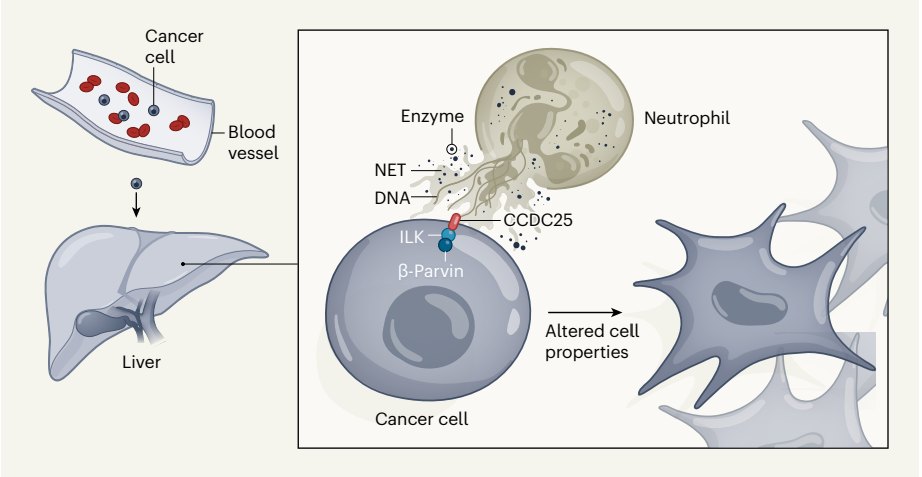

Figure 1 | A process that aids the spread of cancer cells. Cancer-cell migration (metastasis) from the primary site of growth, through the bloodstream, to a secondary site requires supportive signals in that distant organ. From their study of mice and samples from people with cancer, Yang *et al.*[1] identify a mechanism that enables cancer cells to metastasize to the liver. Before metastatic cancer cells arrive in the liver, immune cells there called neutrophils extrude a structure called a neutrophil extracellular trap (NET), which contains DNA and enzymes that kill microorganisms. Yang and colleagues report that this structure binds to a protein called CCDC25 on the cancer-cell surface. This interaction triggers a signalling cascade in the tumour cell that is mediated by the enzyme ILK and its partner, the protein β-parvin. This pathway modifies characteristics of the cancer cell and alters actin filaments in the cytoplasm (not shown) that affect cell shape. The changes that occur increase the cancer cell's adhesive and invasive properties and boost its proliferation.

Yang *et al*. show that the ability of NET DNA to foster metastasis to the liver was not specific to breast cancer cells. NETs were observed in liver metastases in people with colon cancer and in tumours arising in the livers of mice that had been injected with human colon cancer cells. The authors found that if human breast and colon cancer cells were engineered to increase their levels of CCDC25, this helped to fuel liver metastasis in mice given such cells. Crucially, the authors identified a correlation between high CCDC25 abundance in primary tumours and shorter long-term survival in patients across multiple cancer types, indicating that monitoring CCDC25 expression might be useful for predictive purposes.

Future studies will be needed to assess the feasibility of targeting CCDC25 for anticancer therapy. The expression of CCDC25 in different cell types and its possible functions in normal cells should be examined. Given that the authors have identified the precise extracellular portion of CCDC25 that interacts with NET DNA, it might be possible to develop specific inhibitors to block this interaction. Such a targeted approach would have the advantage of preserving other functions of NETs that help to fight infections.

It remains to be determined why the liver is particularly prone to NET accumulation compared with other metastatic sites. In the context of mammalian intestinal cancer, the release of NETs from neutrophils is linked to upregulation of a protein called complement C3a, which is mainly produced in the liver, and which can bind to a receptor on neutrophils[7]. Activation of the complement pathway occurs in the mammalian liver before the development of liver metastasis[8], and so a complement-dependent stimulation of NET formation could be hypothesized. However, the specific mechanism involved remains to be elucidated.

Yang and colleagues' findings represent a key advance in efforts to curb cancer spread, and might lead to the development of a specific strategy to halt NET boosting of cancer metastasis. Moreover, the data presented point to a possible way to predict metastasis to the liver by monitoring NET DNA in the blood.

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