substantially reduce these losses and further limit photon absorption in the electrodes.

By optimizing their device in this way, Ahn *et al.* were able to achieve electrically excited emission with the intense brightness and narrow wavelength spectrum characteristic of optical amplification. They also observed that the device enhanced several of the light's properties, including its polarization, coherence (the degree to which the light waves are in step with each other) and directionality (the degree to which the light is emitted in a single direction). These features indicate that the bright light emanating from the edge of the authors' device is a result of amplified spontaneous emission – a key step towards lasing.

Amplified spontaneous emission has already been achieved with nanocrystals through optical excitation, and been used extensively in laser devices in the past two decades. Electrically driven spontaneous emission has also been realized – in fact, it forms the basis of the common light-emitting diode (LED). However, Ahn and colleagues' device is the first to reach the amplified regime. And its nanocrystals can be deposited simply (using a process similar to inkjet printing, for example), thereby avoiding the high-temperature and vacuum conditions required to deposit the crystals used in conventional semiconductor devices.

However, amplified spontaneous emission differs in several aspects from laser emission. To realize an actual laser, Ahn and co-workers would need to narrow the spectrum of emission from their device, lengthen the time over which the light maintains coherence and ensure that the beam is less divergent. To achieve this, they would need to add a device known as a resonator structure, which is beyond the scope of the present work. The output of the device is currently far from that exhibited by conventional semiconductor lasers, but it's important to note that such lasers have been improved by researchers in industry and academia continually over the past six decades. Even so, because such lasers rely on specific semiconductor materials of high quality, there are limits to their versatility in terms of how easily they can be integrated into electronic devices, and the wavelength (colour) ranges that are available.

This is where electrically driven nanocrystal lasers could shine. It could well be that future use of nanocrystals will not be restricted to bright display screens, but might involve other applications that require lasers[9], such as compact sensing or communication. Ahn and colleagues' achievement in realizing electrically driven optical amplification of semiconductor nanocrystals could also inspire researchers working on organic lasers, from which the authors derived some inspiration of their own. In any case, whether they are made from colloidal quantum dots or organic materials, such unconventional integrated lasers driven exclusively by electricity would indeed be a game-changing technology.

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Tumour biology

Enzyme lights dual fires to promote cancer

Anghesom Ghebremedhin & Judith A. Varner

Tumours with certain cancer-driving mutations are difficult to treat. A discovery that one enzyme both controls proliferation and suppresses anticancer immune defences presages the exploration of new cancer-therapy strategies. **See p.139**

The legendary forces of the Universe – such as fire and water, or light and darkness – are in perpetual balance, and in mythology, disruptions in this balance cause mayhem. In cells, disruption in the delicate balance between two opposing types of enzyme, kinase and phosphatase, also leads to chaos. Kinases light cellular signal flares by adding phosphate groups to targeted proteins, and this action is doused by phosphatases, which remove the phosphates. One such opposing pair is the kinase PI3Kβ and the phosphatase PTEN, which together profoundly affect cellular and organismal fate. On page 139, Bergholz *et al.*[1] demonstrate that an imbalance between PI3Kβ and PTEN not only drives proliferation of tumour cells, but also strongly promotes tumour evasion of immune-system defences, leading to breast cancer progression and resistance to state-of-the-art cancer immunotherapy. The authors show how powerful tumour-promoting mutations can initiate signalling cascades that stimulate tumour-cell proliferation and immunosuppression, and identify a single therapeutic strategy that can control both pathways.

"This insightful work shows how loss of the PTEN protein controls both tumour immunosuppression and proliferation."

One of the most common cancer-promoting (driver) mutations in people who have tumours results in the loss of PTEN, a tumour suppressor[2]. PTEN loss allows unchecked PI3Kβ signalling, which leads to the survival and proliferation of tumour cells and results in cancer growth[3]. However, aberrant cell proliferation alone is not usually sufficient to promote tumour development – a cancer must also have strategies for withstanding a barrage of hostile attacks by the immune system that can kill tumour cells. Aggressive tumours can evade the immune system (immune evasion) in three ways: by establishing barriers that prevent cell-killing immune cells called cytotoxic T cells from entering tumours; by overstimulating cytotoxic immune cells (resulting in a dysfunctional immune-cell response termed exhaustion); or by activating immune cells that dampen the immune response. However, little is known about how most tumours directly promote such immunosuppression.

Through comprehensive studies of mouse PTEN-deficient breast cancer cell lines grown *in vitro*, Bergholz and colleagues show that PTEN loss activates PI3Kβ, which directs a bifurcated signalling pathway: one branch promotes tumour growth by signalling through a kinase called AKT to boost cellular survival and proliferation; the other enables immunosuppression mediated by a transcription factor called STAT3 (Fig. 1).

STAT3 has well-characterized roles in repressing the expression of pro-inflammatory signalling molecules called cytokines, and in promoting the expression of immunosuppressive cytokines[4,5]. The authors report that the inhibition of PI3Kβ or STAT3 by gene

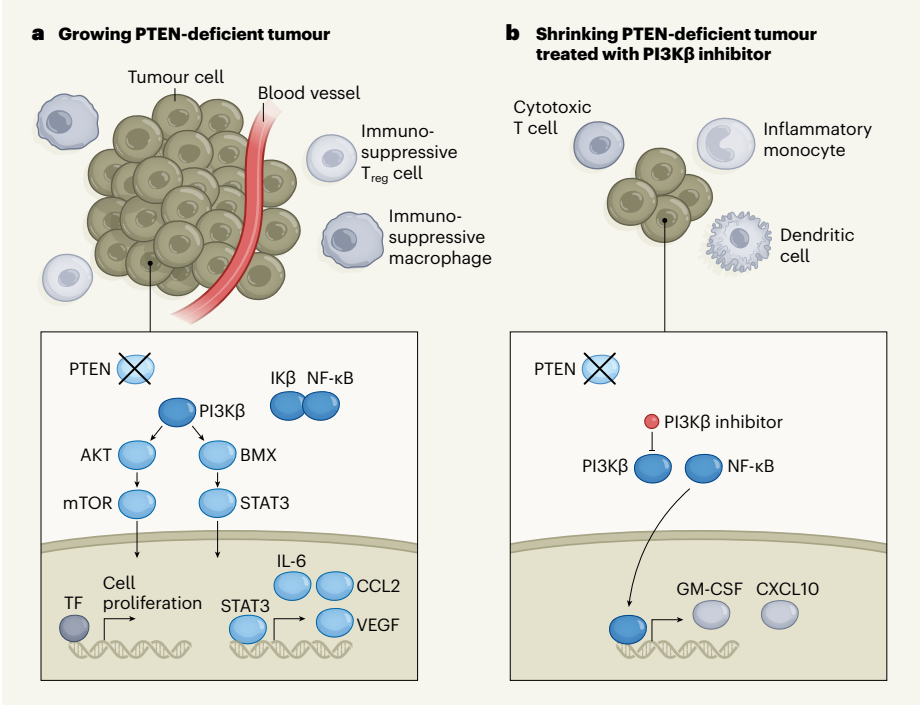

Figure 1 | The enzyme PTEN suppresses immune responses to tumours. a, The protein PTEN, a type of enzyme called a phosphatase, counteracts the activity of PI3Kβ, another enzyme type called a kinase. PTEN is absent in many cancers. Bergholz *et al.*[1] reveal that PTEN loss, which promotes PI3Kβ-mediated pathways that boost cell proliferation, also has a role in blocking immune-cell defences against the tumour. The promotion of cell proliferation occurs through a pathway that includes the proteins AKT and mTOR and various transcription factors (TFs). The immunosuppressive pathway requires the proteins BMX and STAT3, and results in the expression of genes encoding the proteins IL-6, CCL2 and proteins of the VEGF family. Immunosuppressive immune cells (T_{reg} cells and macrophages) are recruited, and blood-vessel formation is also promoted. The transcription factor NF-κB does not enter the nucleus because it is in a complex with the kinase IκB. **b**, When such a tumour is treated with an inhibitor of PI3Kβ, NF-κB is no longer held in check by IκB, resulting in NF-κB-mediated gene expression of the proteins GM-CSF, CXCL10 and other inflammatory molecules. This leads to the recruitment of various immune cells (dendritic cells, inflammatory monocytes and cytotoxic T cells), which results in the destruction of tumour cells.

deletion or by using a small-molecule inhibitor resulted in a rise in the expression of cytokines and immune-cell-activator proteins called chemokines. These factors included CXCL10 and GM-CSF, which can recruit and activate a variety of immune cells: T cells, dendritic cells and monocytes.

The inhibition of PI3Kβ or STAT3 also resulted in a rise in the expression of genes such as *Psme3* and *Psmc5*, which are required for the processing and presentation of peptide fragments called antigens. Antigen presentation is required to trigger immune responses. Genes whose expression levels dropped instead included *Ccl2*, *Il6* and vascular endothelial growth factors (*Vegfa*, *Vegfb*, *Vegfc* and *Vegfd*). These downregulated genes promote tumour growth, blood-vessel development or immunosuppression.

Inhibition of PI3Kβ or STAT3 in mice stimulated the recruitment of cytotoxic immune cells, antigen-presenting dendritic cells and pro-inflammatory monocytes, leading to potent tumour targeting and inhibition. The administration of a pharmacological inhibitor of PI3Kβ together with a leading immunotherapy that targets the immunosuppressive protein PD-1 eradicated breast tumours and established immune memory in mice, in which memory T cells 'remember' previous encounters with tumour-cell antigens and launch a defence response targeting tumour cells that express these antigens. This insightful work shows how PTEN loss controls both tumour immunosuppression and proliferation by permitting PI3Kβ to light signalling fires unchecked. PI3Kβ inhibitors restore balance to this cancer-cell universe by reversing the immunosuppression and out-of-control proliferation.

Because PTEN loss is one of the most common drivers across all types of cancer, identifying molecules that drive immune evasion in PTEN-deficient tumours, and creating therapies that target them, is of paramount importance. It is not clear which of the downstream targets of the PI3Kβ–STAT3 signalling pathway are crucial for promoting PTEN-deficient tumour immunosuppression. Is the key target chemokines (such as CCL2) that recruit immunosuppressive macrophages; factors such as VEGFA that stimulate the formation of blood vessels to support proliferating tumour cells; or pathways that promote immunosuppression by modulating T-cell-suppressive 'checkpoints', such as those mediated by PD-1? Future experiments using methods that reduce the level of these factors might answer this question.

People who have inherited *PTEN* mutations have a fourfold higher risk of developing breast cancer than do individuals who lack such mutations[5]. Could new predictive biomarkers of cancer risk, progression or response to therapy be developed on the basis of the information presented by Bergholz and colleagues? Perhaps coordinated expression levels of PTEN, PI3Kβ, STAT3 or chemokines and cytokines will be predictive of disease status in people with breast cancer. Because PTEN loss confers resistance to treatment with trastuzumab, an antibody that targets the protein HER-2 (which is expressed at high levels in some breast cancers)[6], this raises the question of whether combining trastuzumab and PI3Kβ inhibitors might yield therapeutic benefits.

In contrast to inhibition of the related protein PI3Kα, PI3Kβ inhibition does not increase blood glucose levels, but it does suppress cholesterol biosynthesis and promote metabolic stress[7]. Perhaps targeting PI3Kβ exploits a metabolic dependency of tumour cells that contributes to therapeutic benefit by inducing cellular stress; consideration of these extra pathways might guide future studies of biomarkers and combination therapies for this class of agent. It is now clear that therapeutic targeting of PI3Kβ can restore balance to the tumour-cell universe by counteracting PTEN loss and reversing cancer immunosuppression.

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