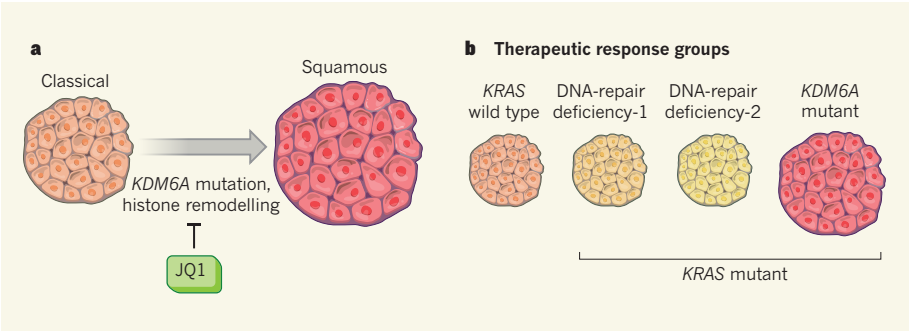

Figure 1 | KDM6A protein in pancreatic cancer. **a**, Pancreatic ductal adenocarcinomas (PDACs) can be catagorized into two main subtypes: classical tumours and more-aggressive, squamous tumours. Andricovich *et al.*[5] have provided evidence from mice and humans that mutations in the gene *KDM6A* cause changes in the patterns of molecular modifications to histone proteins, around which DNA is packaged. This histone remodelling leads to the expression of genes associated with squamous PDAC. However, the authors show that treatment with a small molecule called JQ1 prevents this subtype switch. **b**, This finding adds to the list of PDAC subgroups that can be targeted with drug treatments. Most PDAC tumours involve mutations in the gene *KRAS*, which cannot be targeted by drugs, but some *KRAS* wild-type tumours lack this mutation and carry other mutations that can be targeted. In addition, two subgroups of *KRAS*-mutant tumours carry defects in DNA-repair pathways, which can be targeted by different drugs.

the position of the COMPASS-like complex, enabling other enzymes to modify histones. The authors also showed that the increase in the reach and activation of super-enhancers led to the activation of genes involved in squamous-subtype-like differentiation.

Because *Kdm6a*-mutant PDAC in mice was not associated with significant H3K27me3 demethylation, the authors hypothesized that the alternative functions of the aberrant COMPASS-like complex promoted PDAC, and might therefore be vulnerable to drug treatment. This hypothesis is supported by the fact that mutant UTY, which helps to drive PDAC in males, lacks demethylase activity. Andricovich *et al.* therefore analysed the ability of various drugs that target other histone modifications to prevent the growth of *KDM6A*-deficient human cancer cells *in vitro*.

The authors found that cells harbouring mutations in *KDM6A* or other genes of the COMPASS-like complex were highly sensitive to inhibitors of BET-family proteins. These proteins bind to histone lysine residues that have been modified by acetyl groups, and recruit the cell's transcriptional machinery to promote gene expression. Various studies[6] have shown that BET inhibitors can displace the BET protein BRD4 from acetylated lysines at super-enhancer regions, thereby reducing the expression of cancer-causing genes (oncogenes) such as *MYC*. Because *KDM6A* mutations lead to altered lysine acetylation at super-enhancers, it makes sense that these drugs could be effective in this setting. Indeed, Andricovich *et al.* showed that the BET inhibitor JQ1 decreased BRD4 binding to the super-enhancers that regulate *MYC* and other oncogenes, and so decreased the expression of these genes.

Finally, the authors demonstrated that this drug treatment was also effective *in vivo*. The tumours of *Kdm6a*-deficient mice treated with JQ1 were smaller than those of mice that did not receive the drug, and had well-differentiated features typical of the classical PDAC subtype. This indicates that BET inhibitors have the potential to reverse the effects of the histone-modification remodelling that occurs in the squamous subtype (Fig. 1a). Targeting histone modifications and altered gene-regulatory networks to cause a 'class switch' to a more differentiated, less aggressive subtype of cancer might provide a promising therapeutic strategy. In support of the idea that modulating these factors can alter cancer progression, other studies have shown that enhancer reprogramming and large-scale losses of DNA methylation play a part in the spread of cancer[7,8].

Our increased understanding of the molecular underpinnings of cancer has hugely improved treatments for many tumours, although in PDAC the relative lack of obvious drug targets has presented a challenge. There are some cases of PDAC that involve oncogenes for which inhibitors do exist[9]. However, most PDAC tumours harbour oncogenic mutations in the gene *KRAS*, for which inhibitors are not available. But there are two clear groups of people with *KRAS*-mutant PDAC tumours characterized by deficiencies in specific DNA-repair pathways that can be targeted by drugs[10,11] (Fig. 1b). Patients harbouring *KDM6A* mutations (and possibly other mutations in genes of the COMPASS-like complex) might represent another subgroup, who would benefit from therapies targeting BET function. Moreover, BET inhibitors could have broader activity if combined with other inhibitors of histone remodelling, as previously reported[12].

It is to be hoped that more molecular biomarkers will soon be discovered that, like *KDM6A* mutations, can predict tumour responsiveness to a particular therapy. This research avenue provides cause for optimism that improved outcomes for people with pancreatic cancer will be the norm — and not the exception — in the near future. ■

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CONDENSED-MATTER PHYSICS

Plasmon propagation pushed to the limit

Excitations called plasmons have the potential to miniaturize photonic devices, but are often short-lived. Microscopy reveals that plasmons in the material graphene can overcome this limitation at low temperatures. SEE LETTER P.530

JUSTIN C. W. SONG

Light can be confined and steered at the nanoscale using collective oscillations of electrons known as plasmons. But just as death and taxes are the only certainties in life, energy loss is the only certainty in plasmonics. The tighter the confinement of light, the shorter the lifetime of the plasmons[1] — a trade-off that is a major hurdle in the practical use of these oscillations. On page 530, Ni *et al.*[2] use a technique called scanning near-field optical microscopy to study plasmons in a single layer of carbon atoms known as graphene,

at cryogenic temperatures (60 kelvin). The authors show that the plasmons can produce extremely compact light confinement while retaining long lifetimes. They use their results to determine the fundamental limits of plasmon propagation in graphene.

The propagation of light involves the oscillation of electric and magnetic fields. This oscillation defines the relationship between the frequency and wavelength of light, and underpins the diffraction limit — the fact that, in free space, light spreads out if it passes through a region narrower than its wavelength. When light interacts with plasmons, its speed can be substantially reduced, which allows it to be confined to distances much smaller than its free-space wavelength. As a result, plasmons have become a versatile tool for controlling the behaviour of light at the nanoscale[3]. However, the same light–plasmon interaction that can confine light below its wavelength also enables energy to be lost through the scattering of electrons.

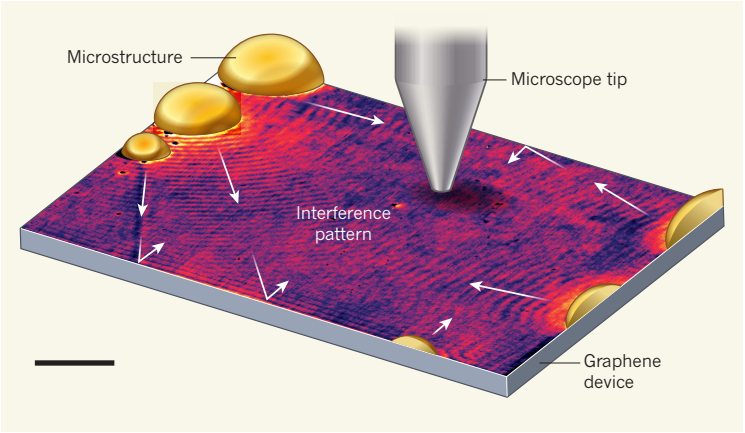

Figure 1 | Low-temperature plasmons investigated in graphene. Ni *et al.*[2] used an instrument known as a scanning near-field optical microscope to study exotic excitations called plasmons. They used the narrow metallic tip of the microscope to launch plasmons in a device containing the material graphene, at cryogenic temperatures (60 kelvin). The authors then scanned the tip across the device to image the interference pattern produced by the plasmons as they were reflected (white arrows) from the edges of the device and from microstructures present on the device's surface. The interference pattern consisted of bright and dark bands that were found throughout the device, demonstrating that the plasmons could travel several micrometres before their energy was lost. Such long-lived plasmons could have many applications. Scale bar, 1 μm. (Adapted from Fig. 1c of ref. 2.)

Noble metals such as silver and gold are conventionally used in plasmonics, but suffer from high losses. In the past few years, 2D materials have become promising alternatives[4]. In the case of graphene, plasmons can compress light to distances as small as one-three-hundredth of the light's free-space wavelength[5]. Furthermore, the electron density of graphene can be readily controlled, which provides direct electrical means of tuning the properties of the plasmons. But although sustained efforts to improve the quality of graphene have yielded steady advances[6], plasmon loss remains substantial.

In a bid to push the limits of plasmon propagation, Ni and colleagues launched and imaged plasmons in a device containing high-quality graphene at cryogenic temperatures. The use of these temperatures minimized losses caused by temperature-sensitive processes, such as the scattering of electrons from mechanical vibrations called phonons. The authors customized an instrument known as a scanning near-field optical microscope so that it could operate at cryogenic temperatures. Although these instruments are routinely used to study plasmons at room temperature, operating them at lower temperatures has been difficult.

Ni *et al.* used the narrow metallic tip of the microscope to launch plasmons in the graphene device. They then scanned the tip across the device to image the interference pattern produced by the plasmons as they reflected from the edges of the device and from microstructures present on the device's surface (Fig. 1). This technique is particularly useful because it launches plasmons in the interior of the device, which limits losses caused by interaction with the device's edges. Such losses can be large in other approaches[7].

The fruits of Ni and colleagues' labour are pronounced plasmon interference fringes (bright and dark bands) that are found throughout the device and that extend several micrometres from any boundaries. These fringes make the entire device 'light up' with a characteristic washboard-like pattern. The plasmons simultaneously have relatively long lifetimes (reaching 1.6 picoseconds; 1 ps is 10^{-12} seconds) and confine light to distances smaller than one-sixtieth of the free-space wavelength. Their quality factor, a measure of energy retention, is 130, which is a record for plasmons that enable such compact light confinement. The performance of the plasmons therefore bucks the trade-off between tight confinement and high loss. It is possible thanks to the extremely high quality of the authors' graphene device, which contains highly mobile electrons that can travel several micrometres without scattering.

Remarkably, using a combination of detailed modelling and systematically collected temperature-dependent data, Ni and colleagues determined that the main cause of energy loss at low temperatures was not electron scattering in the graphene. Instead, plasmon loss arose mostly from insulating material that surrounded the graphene. The quality of the plasmons could therefore be improved by reducing these extrinsic losses, for example by altering this insulating material. The authors also suggest that the intrinsic (fundamental) limits of plasmon propagation at cryogenic temperatures have not yet been reached. They calculate that it might be possible to achieve quality factors more than seven times higher than the one reported in the current paper.

Nevertheless, the exceptional quality of Ni and colleagues' graphene plasmons sets a new standard for nanophotonic platforms. Tightly confined light in such plasmons can now be thought of as being highly stable, with the ability to be directed and steered across distances of several micrometres. The possibilities for the future are vast and range from the fundamental (such as probing the topological[8] and geometrical structure[9] of plasmons) to the applied (including nanoscale plasmon lasers[10], sensitive light detectors, sub-wavelength routing of light, and nanoscale optical interconnects[3]). The authors' high-quality graphene plasmons, combined with recently developed techniques to substantially reduce the overall size of plasmons[11], make a compelling case for graphene-based nanophotonics.

Perhaps most exciting, however, is the prospect of using scanning near-field optical microscopy at cryogenic temperatures to probe excitations other than plasmons. Phases of matter such as superconductors, ferromagnets and antiferromagnets possess excitations that could be accessed using this technique[12]. In the past few years, a wide range of these phases has been discovered on 2D materials, on which the surfaces are fully exposed and are therefore easily accessible. Such phases manifest only at low temperatures, making cryogenic operation the key to launching the excitations and studying their intricate dynamics. ■

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