α-synuclein to cellular material that had been isolated from ruptured oligodendrocytes or neurons, the oligodendrocytic homogenate caused the protein to aggregate into a strain of greater seeding potency than did the neuronal homogenate. Some as yet unidentified factors in oligodendrocytes, then, seem to drive the formation of the MSA strain.

Collectively, the authors' experiments show that oligodendrocytes produce a structural variant of α-synuclein that robustly seeds aggregation in both oligodendrocytes and neurons. However, the cell type strongly influences the molecular strain of the aggregates that forms: oligodendrocytes specifically generate the MSA strain, whereas neurons preferentially produce the LBD strain (Fig. 1). The authors conclude that cell-type-specific factors regulate the molecular architecture and distinctive harmful properties of aberrant α-synuclein aggregates. They further suggest that the robust seeding capacity of the MSA strain contributes to the aggressive clinical progression of MSA.

The recognition that different cells generate different disease-causing protein strains raises a wealth of questions. An especially perplexing problem is how such large amounts of α-synuclein end up in oligodendrocytes in MSA, given that these cells do not produce much of the protein[9]. Possible mechanisms include augmented oligodendrocytic expression of α-synuclein in the disease state, or the uptake of α-synuclein that has been released from neurons[10].

MSA can affect different brain systems in people with the condition[3]. Peng and colleagues' findings demonstrate the possible role of cell composition in these differences, but what other factors might be involved? Perhaps the metabolism of α-synuclein in neurons and oligodendrocytes varies between brain regions. Or maybe the regional vulnerability to α-synuclein deposition is dictated mainly by where seeding first occurs. Two other types of neuron-supporting cell, astrocytes and microglia, are also involved in MSA, but their roles in the disease remain to be defined[11]. Finally, the role of small, toxic α-synuclein assemblages called oligomers[12], which might act in different brain regions from the larger aggregates, needs further exploration. Clarification of these issues could improve our understanding not just of α-synuclein diseases, but also of other neurodegenerative disorders that involve protein aggregation.

In sum, the authors' work highlights the interplay between a cell's composition and proteins that can cause disease. Identification of the cell-specific factors that impel α-synuclein to aggregate into the MSA strain could reveal ways to treat this debilitating and ultimately fatal brain disorder. Peng and colleagues' findings are also a salutary reminder of the salient part played by non-neuronal cells in both the health and failure of the nervous system. ■

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CANCER

Subtype switch foils pancreatic tumours

Mutations in the gene *KDM6A* drive an aggressive subtype of pancreatic cancer by causing repositioning of an enzyme complex that modifies histone proteins associated with DNA, leading to altered gene expression.

FIEKE FROELING & DAVID TUVESON

Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadly cancers in Western society[1] because it tends to be diagnosed late and responds poorly to therapy. PDAC tumours fall into two main groups[2–4]: a 'classical' subtype, and a more aggressive 'squamous' subtype in which pancreatic cells fail to undergo proper differentiation. The squamous subtype often involves mutations in members of the COMPASS-like complex — a group of methyltransferase and demethylase enzymes that, respectively, add or remove methyl groups from lysine amino-acid residues on histone proteins, around which DNA is packaged. Such histone modification can lead to changes in the expression of histone-associated genes involved in pancreatic-cell differentiation. Writing in *Cancer Cell*, Andricovich *et al.*[5] demonstrate the role of mutations in one member of this complex, KDM6A, in driving the squamous PDAC subtype.

The *KDM6A* gene is found on the X chromosome, and, in males, the presence of a *KDM6A* mutation can co-occur with mutation of a related gene on the Y chromosome, *UTY*. Andricovich *et al.* found that *KDM6A* and *UTY* mutations were associated with the squamous subtype of PDAC, and with shortened length of patient survival. They then used mouse models to confirm that functional KDM6A acts to suppress the development of PDAC. Mice harbouring *Kdm6a* gene mutations developed aggressive, poorly differentiated squamous tumours that showed protein- and gene-expression patterns characteristic of human tumours of the squamous subtype[2]. These defects were more pronounced in females than in males, consistent with the fact that females carry two copies of *Kdm6a* in their cells and males have one copy of *Kdm6a* on the X chromosome and *Uty* on the Y.

KDM6A is a demethylase that removes a methyl modification dubbed H3K27me3 from lysine residue 27 on histone H3 proteins. But Andricovich and colleagues found that only a small percentage of H3K27me3 marks were altered in cells from *Kdm6a*-mutant mice, compared with controls. This observation led the authors to posit that altered KDM6A demethylase activity was not the driver of *Kdm6a*-mutant PDAC. Instead, they found that loss of *Kdm6a* resulted in changes in other histone modifications, specifically at groups of gene-regulatory DNA sequences called super-enhancers, whose activation promotes the expression of certain genes that are highly expressed in PDAC.

In particular, the researchers observed changes in the distribution across super-enhancers of a different methyl modification (dubbed H3K4me1) and a modification involving acetyl groups at lysine 27 of histone H3 (H3K27ac). Such changes were associated with a repositioning of the COMPASS-like complex to these regions. The authors found that the altered histone modifications led to activation of some super-enhancers, and, in some cases, to an increased reach — an ability to regulate distant genes that the super-enhancer cannot normally influence. These findings indicate that KDM6A exerts its tumour-suppressive role not only through its demethylase activity, but also by altering

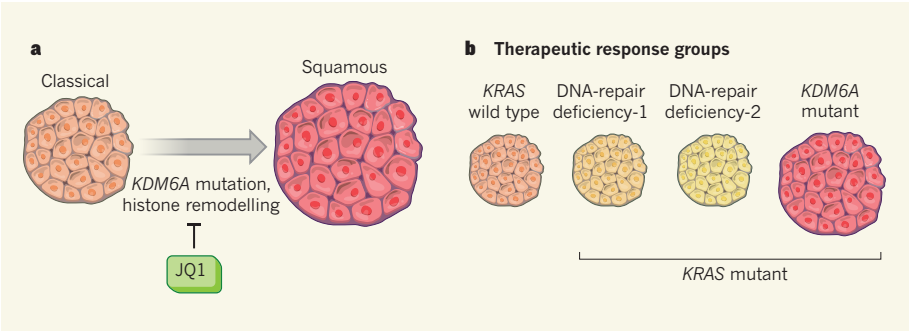

Figure 1 | KDM6A protein in pancreatic cancer. **a**, Pancreatic ductal adenocarcinomas (PDACs) can be catagorized into two main subtypes: classical tumours and more-aggressive, squamous tumours. Andricovich *et al.*[5] have provided evidence from mice and humans that mutations in the gene *KDM6A* cause 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,