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PANCREATIC CANCER

The COMPASS shows the way

> deregulation of the COMPASS-like complex is key for squamous PDA development

Mutation of lysine demethylase 6A (*KDM6A*) on the X chromosome has been linked to pancreatic tumorigenesis, but the functional consequences of this are unknown.

Using available cancer genomics databases and cancer cell lines, Andricovich et al. determined that mutation or loss of *KDM6A* is common in pancreatic ductal adenocarcinomas (PDAs) of the squamous subtype in females. Interestingly, in male patients, squamous PDAs also showed loss or reduced expression of *UTY*, the Y chromosome homologue of *KDM6A*, which encodes a protein that lacks demethylase activity. Mutations or loss of these genes correlated with shorter patient survival, which suggests that their normal function is in tumour suppression. KDM6A and UTY are part of the complex of proteins associated with SET1 (COMPASS)-like complex, which mono-methylates histone H3 lysine 4 (H3K4me1) to define the boundaries of enhancers, which can become super-enhancers (SEs) upon H3K27 acetylation (H3K27ac); this activity does not require the demethylase activity of KDM6A, and so it seems likely that any role in tumorigenesis relates to enhancer regulation.

To examine the function of KDM6A in PDA formation, the authors crossed *Kdm6a*-null mice with mice expressing $Kras^{G12D}$ in the pancreas (driven by either *Pdx1–Cre* or *Ptf1a–Cre*). In female mice, *Kdm6a* loss accelerated the development of $Kras^{G12D}$-driven tumours with squamous features. Tumours did develop in males, but they were less aggressive and lacked squamous features; however, there were squamous tumours in two of nine males that also had loss of *Uty*, supporting the importance of non-demethylating activities of these proteins in squamous tumour formation.

Transcriptome analyses showed substantial changes in cell lines established from tumours of *Ptf1a–Cre*;$Kras^{G12D}$;$Kdm6a^{fl/fl}$ female mice compared with those expressing *Kdm6a*; by contrast, cells from *Ptf1a–Cre*;$Kras^{G12D}$;$Kdm6a^{fl/Y}$ tumours in males did not have clear gene expression changes. Specifically, female tumours gained expression of the ΔNp63 isoform of *Trp63* and lost *Sox17* and *Pdx1* expression, which are all hallmarks of squamous PDAs. Mapping of enhancer chromatin (through examining H3K4me1 and H3K27ac distribution) indicated that some SEs were specifically activated in tumour cells from *Kdm6a*-null female mice. These SEs were linked to upregulation of the transcription factors p63, MYC and RUNX3 and the pathways they control, as well as pathways controlled by bromodomain-containing protein 4 (BRD4), an enhancer chromatin reader. Furthermore, re-expression of demethylase-deficient KDM6A or UTY was sufficient to downregulate p63 and MYC and reduce cell growth, supporting the hypothesis that deregulation of the COMPASS-like complex is key for squamous PDA development.

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Screening of human PDA cell lines for sensitivity to 78 small-molecule inhibitors of epigenetic regulators indicated that KDM6A-null cells were sensitive to bromodomain and extraterminal (BET) inhibitors. The BET inhibitor JQ1 decreased activation of BRD4-controlled pathways, as well as the expression of MYC, p63 and RUNX3 and the activation of their downstream pathways. Treatment of *Ptf1a– Cre*;$Kras^{G12D}$;$Kdm6a^{fl/fl}$ female mice with JQ1 beginning at 3 weeks of age prevented development of squamous PDAs; interestingly, JQ1 also prevented growth of PDAs in male *Ptf1a–Cre*;$Kras^{G12D}$;$Kdm6a^{fl/Y}$ mice, indicating that, perhaps, some biological effects of JQ1 are not specific to the squamous subtype.

These data highlight the importance of SE reprogramming in PDA development as well as gender-specific differences in tumorigenesis. Although it is unclear whether treatment of established tumours would have therapeutic effects, further investigation of this possibility is warranted.

Sarah Seton-Rogers

ORIGINAL ARTICLE Andricovich, J. et al. Loss of KDM6A activates super-enhancers to induce gender-specific squamous-like pancreatic cancer and confers sensitivity to BET inhibitors. *Cancer Cell* **33**, 512–526 (2018)