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EDITORIAL

ATRX Links Chromatin Remodeling to Inflammation and Tumorigenesis in the Pancreas

A link between inflammation and cancer is clear, yet the details of how each influences the other remain incomplete. Young et al[1] have added new insight implicating a link between inflammatory responses and chromatin remodeling in susceptibility to neoplastic changes in the pancreas. Studying mouse models of pancreatic inflammation and of pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, Young et al[1] found that the ATRX chromatin remodeling protein is critical both to suppress pancreatitis in response to damage and to suppress progression to precancerous neoplastic lesions in the presence of the $Kras^{G12D}$ oncogene. Intriguingly, this suppression was specific to female mice and possibly to female human patients.

Inflammation in the pancreas is a clinically important problem, with acute pancreatitis resulting in severe morbidity and mortality. Under unchallenged conditions, ATRX was dispensable for adult pancreatic homeostasis in mice. However, after cerulein-induced mild pancreatitis, loss of ATRX increased tissue damage and allowed the development of fibrosis and epithelial metaplasia, phenotypes consistent with transition from acute pancreatitis to chronic pancreatitis.[1] Notably, this ATRX dependence was observed predominantly in female mice, whereas loss of ATRX had only a minimal effect on the male pancreas. Thus, the ability to repair and/or maintain intact chromatin is critical for re-establishing homeostasis after pancreatic damage via utilization of sex-specific regulatory events.

The etiology of PDAC remains uncertain, in part owing to the inability to diagnose early stage disease in human beings. Although a number of lifestyle factors are linked to a slight increase in risk, chronic pancreatitis is by far the most profound nongenetic risk factor for PDAC.[2] Activating mutations in the *Kras* oncogene are found in >90% of PDAC cases, but a wide body of literature indicates that this mutation alone is not sufficient for the development of cancer. Cerulein-induced pancreatitis is sufficient to drive the development of precancerous benign precursors called pancreatic intraepithelial neoplasms (PanINs) in *Kras* mutant mice.[3] Young et al[1] hypothesized that ATRX could function in suppression of $Kras^{G12D}$-initiated tumorigenesis because of its ability to suppress chronic pancreatitis and re-establish homeostasis in response to mild pancreatitis. Indeed, loss of ATRX greatly accelerated the development of precancerous neoplastic lesions in female pancreata expressing $Kras^{G12D}$, even without induction of pancreatitis by cerulein treatment. In male mice, just as loss of ATRX had little effect on cerulein-induced pancreatic damage, loss of ATRX also had little effect on $Kras^{G12D}$-initiated tumorigenesis.[1] When adult mice were induced to express $Kras^{G12D}$ and delete *Atrx* (via tamoxifen-regulated Cre-mediated recombination), female pancreata underwent fibrosis and acinar-to-ductal metaplasia, similarly to that seen in response to cerulein-induced damage without $Kras^{G12D}$ mutation. However, in the presence of $Kras^{G12D}$, these epithelial metaplastic lesions progressed to PanINs in female mice but not in male mice. Male mice with $Kras^{G12D}$ expression and loss of *Atrx* had mild fibrosis and epithelial metaplasia, as was seen with $Kras^{G12D}$ mutation alone, but were unable to progress to PanIN formation within the 2-month time period studied. Thus, the ability to repair and/or maintain chromatin efficiently provides a mechanism enabling pancreatic cells to resist neoplastic transformation in the presence of $Kras^{G12D}$ mutation. Unfortunately, these mice could not be followed up long enough to determine if loss of ATRX allowed progression to carcinoma because of obstructive tumors developing in the oral cavity. Thus, it remains to be seen if ATRX also suppresses the ability of noninvasive precursors to progress to carcinoma.

This mechanistic work on mouse models was supported by the occurrence of *ATRX* mutations in human PDAC. In a study of 729 PDAC patients, 145 were found to contain *ATRX* mutations. A total of 68% of *ATRX* mutations occurred in female patients even though female patients comprised only 42% of the total cases. Most of these mutations occurred in noncoding regions and future work is needed to determine if they affect the expression of this gene. However, 8 patients harbored mutations predicted to affect protein function and 7 of these patients were women. The correlation between *ATRX* mutations and sex did not hold with other cancers, namely pancreatic neuroendocrine tumors or glioblastomas, other tumors shown to carry *ATRX* mutations. The etiology of the sex-specific link in PDAC remains unclear, with sex-specific differences in inflammation or in hormonal regulation 2 possibilities.

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Conflicts of interest
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