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EDITORIAL

EGFR Reloaded: Finding New Ways to Shape Pancreatic Cancer Epigenome

Pancreatic cancer (PC) is a devastating disease predicted to be the second leading cause of cancer deaths in approximately 15 years in the United States.[1] With the rise of PC lethality, understanding of the mechanisms driving initiation and progression of the disease is critical to advance treatments and improve prognoses. PC has well-established highly recurrent mutations in 4 driver genes including the oncogene KRAS, and tumor suppressors TP53, CDKN2A, and SMAD4.[2] Furthermore, different aspects of the role of the previously mentioned driver mutations on PC development have been extensively described for close to 40 years.[2] However, these mutations alone cannot account for PC heterogeneity, discern early from advanced disease, and predict treatment response.[3] For example, 2 consensus PC subtypes with significantly different prognosis, classical and basal, are defined by differential gene expression as opposed to mutational profile.[4,5] Furthermore, PC metastasis is driven by enhancer reprogramming rather than secondary somatic drivers.[6] Thus, supporting the fact that key pathogenic features are largely conferred by the epigenetic make-up of PC. This is particularly important because the identification of epigenetic contributors to PC development is a promising field because of the relative reversible nature of epigenetic changes.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Zhang et al[7] describe a novel interplay controlling PC initiation involving the antagonism of chromatin regulator ARID1A by EGF receptor (EGFR) signaling, a well-known oncogenic cascade driving key pathways promoting PC development and progression.[5,8] The authors define a role for this interplay in modulating acinar-to-ductal metaplasia (ADM), a required initiating step of PC biology.[9] ARID1A is a member of the SWI/SNF chromatin remodeling complex regulating gene transcription to maintain normal cell growth in different tissues.[10–12] Using a pancreas-specific conditional knockout model, the authors show that *Arid1a* depletion promotes acinar-to-ductal transdifferentiation, suggesting ARID1A's role in maintaining normal acinar tissue homeostasis. Furthermore, the manuscript shows that EGFR signaling triggers ARID1A genomic displacement from chromatin-bound to nucleoplasmic fractions, mimicking ARID1A loss-of-function mutations resulting in ADM induction. ARID1A dissociation is associated with local increases in H3K27ac, a chromatin mark associated with transcriptionally active regulatory elements. Thus, loss of ARID1A leaves a chromatin state favoring transcriptional activation. However, the causative effect of EGFR in driving ARID1A genomic displacement requires involvement of NFATc1, an inflammatory transcription factor essential for driving transcriptional activation of ADM-related genes in the absence of ARID1A. Furthermore, the authors determined that downstream of EGFR, NFATc1 acts as the essential link that displaces ARID1A and leads to transcriptional activation of genes involved in ADM. In fact, overexpression of NFATc1 was sufficient to displace ARID1A from the genome, whereas inhibition of NFATc1 maintains ARID1A genomic occupancy and healthy acinar tissue. Genetically engineered mouse model carrying *Nfatc1* and *Arid1a* dual depletion exhibits significantly reduced incidence of ADM and PanIN precursor lesions. The lack of ADM and the unchanged EGFR-pERK axis activity, highlight the requirement of NFATc1 in promoting pancreatic metaplasia in the absence of ARID1A. Thus, EGFR signaling and ARID1A loss results in a transcription state suitable and the driving factor for pancreatic pathogenesis and carcinogenesis.

Overall, this work defines novel molecular events underlying the initiation of PC from an epigenetic lens. As previously mentioned the biologic role of epigenetics changes in the pathogenesis of this disease have been extensively described; however, the underlying mechanistic details involved controlling different PC stages (especially early phases of the malignancy) still remain elusive. Increasing the molecular understanding of this role provides opportunities for early diagnosis approaches or intervention with regimens aimed at preventing tumor development. For instance, one could postulate based on this study's findings that expression changes regulated by the epigenetic loss of ARID1A function may provide new diagnostic tools for early PC detection. Studies have shown that RNA expression in circulating exosomes derived from tumor cells can be a powerful tool to detect malignancies.[13] In this case of ARID1A-dependent regulated gene expression changes could be the foundation of future early PC diagnostic tools.

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References

1. Rahib L, Wehner MR, Matrisian LM, et al. Estimated projection of US cancer incidence and death to 2040. JAMA Netw Open 2021;4:e214708.

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2. Maitra A, Hruban RH. Pancreatic cancer. Annu Rev Pathol 2008;3:157–188.
3. McDonald OG, Li X, Saunders T, et al. Large-scale epigenomic reprogramming during pancreatic cancer progression links anabolic glucose metabolism to distant metastasis. Nat Genet 2017;49:367–376.
4. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531:47–52.
5. Raphael BJ, Hruban RH, Aguirre AJ, et al. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell 2017;32:185–203.
6. Roe J-S, Hwang C-I, Somerville TDD, et al. Enhancer reprogramming promotes pancreatic cancer metastasis. Cell 2017;170:875–888.
7. Zhang Z, Wang X, Hamdan F, et al. NFATc1 is a central mediator of EGFR-induced ARID1A chromatin dissociation during acinar cell reprogramming. Cell Mol Gastroenterol Hepatol 2023, XX:XXX–XXX.
8. Lomberk G, Blum Y, Nicolle R, et al. Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes. Nat Commun 2018;9:1978.
9. Johnson BL, d'Alincourt Salazar M, Mackenzie-Dyck S, et al. Desmoplasia and oncogene driven acinar-to-ductal metaplasia are concurrent events during acinar cell-derived pancreatic cancer initiation in young adult mice. PLoS One 2019;14:e0221810.
10. Guan B, Wang TL, Shih IM. ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. Cancer Res 2011;71:6718–6727.
11. Kuo TL, Cheng KH, Chen LT, et al. ARID1A loss in pancreas leads to islet developmental defect and metabolic disturbance. iScience 2022;26:105881.
12. Blümli S, Wiechens N, Wu MY, et al. Acute depletion of the ARID1A subunit of SWI/SNF complexes reveals distinct pathways for activation and repression of transcription. Cell Rep 2021;37:109943.
13. Schwarzenbach H. The clinical relevance of circulating, exosomal miRNAs as biomarkers for cancer. Expert Rev Mol Diagn 2015;15:1159–1169.

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