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Activated glucocorticoid signaling promotes acinar-to-ductal metaplasia and KrasG12D-driven tumorigenesis in pancreas

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Acinar-to-ductal metaplasia (ADM), an inflammatory lesion associated with replacement of acinar cells by tubular complexes is thought to represent a condition with increased risk of neoplasia. However, the direct evidence linking acinar-to-ductal metaplasia and development of pancreatic neoplasm is still lacking. Glucocorticoid-mediated signaling pathway is known to be a part of the feedback control machinery of immune system that acts to suppress excessive immune activity. In the present study, we explored the role of GR in development of ADM and pancreatic intraepithelial neoplasia (PanIN) in mice with pancreatitis. We initially identified that evaluated levels of activated glucocorticoid receptors (GR) were observed in patients of chronic pancreatitis and pancreatic ductal adeno carcinomas (PDAC). Utilizing mice conditionally expressed KrasG12D in acinar cell with or without loss of GR, we demonstrated that GR activation was required for generation of metaplastic ductal lesion and development of pancreatic intraepithelial neoplasia (PanIN) in mice with experimental pancreatitis. Administration of dexamethasone,a potent synthetic glucocorticoid was sufficient to induce development of PanINs and PDACs in KrasG12D mice that harbored single-allele deletion of p53. We further revealed that non-genomic activation of GR was a key action that led to evaluate c-Src signaling and trigger a pathological threshold of Ras activity necessary for neoplastic transformation. In contrast, treatment of dasatinib, a Src kinase inhibitor suppressed development of PanINs and PDACs induced by dexamethasone. Importantly, Cre-lox based lineage-tracing mice was applied and identified that GR activation directly transformed GFP-tagged KrasG12D-expressing acinar cells to tumorigenic cells. The findings explained why inflammatory ductal reprogramming predisposes to development of pancreatic neoplasm.

Biography

Chia-Ning Shen is serving as the Deputy Director and Associate Research Fellow, Academia Sinica, Taiwan. He is also working as an Associate Research Fellow, Academia Sinica, Academia Sinica, Taipei, Taiwan.

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