The role of the SWI/SNF complexes in pancreatic cancer

Pancreatic ductal adenocarcinoma, known colloquially as pancreatic cancer (PC), is the eighth leading cause of cancer-related mortality worldwide[1]. Due to the aggressive nature of the malignancy, and late detection and diagnosis, the overall five-year survival rate is less than five percent[2]. The SWItch/sucrose non-fermentable (SWI/SNF) complex is a large complex of adenosine triphosphate (ATP)-dependent chromatin remodeling factors that regulates the transcriptional activity of a wide variety of genes involved in cellular growth and differentiation[3,4]. In vitro studies have shown that the SWI/SNF complex is able to unwrap, slide, and eject nucleosomes[5]. In vivo, SWI/SNF has been demonstrated to bind preferentially to promoters and regulatory regions, translocating DNA through ATPase activity and creating space for transcription factor binding[6]. Given that deregulation of transcriptional control is characteristic of many cancers, SWI/SNF has become increasingly studied in recent years for its involvement in the development in cancer. The mammalian SWI/SNF complexes are composed of one of two mutually exclusive catalytic ATPase subunits, either brahma homologue (BRM or SMARCA2) or BRM-related gene 1 (BRG1 or SMARCA4); a set of highly conserved “core” subunits SNF5 (SMARCB1), BAF155, and BAF170; and variant subunits including ARID1A, ARID1B, BAF180 (PBRM1), BAF200 (ARID2), and BRD7 that are thought to contribute to the targeting,

assembly, and regulation of lineage-specific functions of the subunits[6]. Normally, SWI/SNF complexes are enriched at enhancers and promoters of active genes, and regulate differentiation and proliferation in many lineages[7]. As result of many recent studies, SWI/SNF complexes are emerging as tumor suppressors—inactivating mutations in several subunits have been found in a variety of cancers, the first of which was discovered in rhabdoid tumors[8,9]. For example, the SNF5 subunit of SWI/SNF is inactivated via biallelic mutations in nearly all malignant rhabdoid tumors[6]. ARID1A is mutated in 50% of ovarian clear cell carcinomas[10,11]. Furthermore, BRM is absent or expressed at low levels in several tumor types, including lung cancer[6].

Many recent studies have demonstrated that PC might also be a SWI/SNF-dependent cancer[12]. In a 2012 study, using high-resolution profiling (CGH arrays) of 70 pancreatic cancers integrated with gene expression profiling and exon and transcriptome sequencing, Shain et al. found several “hills” in the genomic mutational landscape, converging on all five of the ATPase and DNA-binding subunits of the SWI/SNF complex[13]. For example, SMARCA4 was found to be mutated in only 11% of pancreatic cancer samples, however, taken together, at least one third of PCs possessed alterations of SWI/SNF subunits. Furthermore, re-expression of SMARCA4 in SMARCA4-deficient pancreatic cancer cell lines

led to significantly reduced cell growth, consistent with a tumor-repressive function[13]. Additional mechanistic insight into SWI/SNF tumor suppressive function in PC has emerged from studies describing the antagonistic roles of SWI/SNF and Polycomb group (PcG) proteins—specifically Polycomb Repressive Complex 2 (PRC2). Emerging evidence suggests that EZH2, a subunit of PRC2, is oncogenic. EZH2 is upregulated in several different cancer types, and its expression enhances tumor cell growth[6]. EZH2 is upregulated in SNF5-deficient tumors, and the inactivation of EZH2 blocks the formation of tumors that arise following loss of SNF5[14].

Additional mechanisms of SWI/SNF tumor suppression have also been illuminated. For example, $p16^{INK4A}$, a cyclin-dependent kinase (CDK) inhibitor that regulates the RB tumor suppressor pathway, is downregulated following SNF5 inactivation and has been implicated in tumorigenesis[6]. Furthermore, SWI/SNF complexes can interact directly with MYC, an oncogene frequently expressed in PC. Some SMARCB1-deficient tumors show activation of MYC programs[14,15]. SWI/SNF has been shown to participate in the Hedgehog signaling pathway as well. SWI/SNF directly interacts with GLI1, the effector of hedgehog signaling in rhabdoid tumor cells, and loss of SNF5 leads to overactivation of the Hedgehog-Gli pathway[16].

Because chromatin remodeling has recently been established in propagating DNA damage signals within cells and facilitating access of DNA repair proteins to DNA damage, the role of SWI/SNF in mitigating DNA damage (which can lead to genomic mutation and cancer) has been explored. In a 2014 study, Watanabe et al. demonstrated that GFP-tagged ARID1A and Halo-tagged ARID1B accumulate at the site of laser micro-irradiation-induced DNA damage (inducing DSBs). In addition, suppression of either ARID1A or ARID1B expression significantly reduced the efficiency of DSB repair[17]. Suppression of ARID1A or ARID1B significantly reduces the accumulation of KU70 and KU80 at DSBs, suggesting an essential role in the non-homologous end joining (NHEJ) process. Finally, SWI/SNF complex subunit repression significantly sensitizes cells to IR and cisplatin, a DNA intra- and interstrand crosslinking agent[17]. Thus, PC cells that lack SWI/SNF subunit expression are deficient in DNA repair, suggesting a vulnerability that could be useful for the administration of platins and other cancer therapy drugs.

The familial clustering of pancreatic cancer has been established, with the risk rising as the number of affected first-degree relatives with PC increases[18]. To identify the inherited genetic variants in SWI/SNF that could modify the risk of pancreatic cancer, a recent genome-wide association (GWA) study was performed. Zhu et al. conducted a two-stage, case-control study in a Chinese population to analyze the

association between 14 common variants in 6 SWI/SNF genes (SMARCA4, SMCRB1, PBRM1, BRD7, ARID1, and ARID2) and the risk of PC[12]. Three variants reaching GWA statistical significance—rs11644043 (BRD7), rs11085754 (SMARCA4), and rs2073389 (SMARCA4)—were found in the discovery stage made up of 310 cases and 457 controls, and confirmed in the validation stage (429 cases and 585 controls). In both stages, rs11644043 in BRD7 and rs11085754 in SMARCA4 showed consistent significant association, with discovery stage odds ratios (ORs) and 95% confidence intervals (CI) of 2.04 (1.17-3.56) and 1.64 (1.16-2.33), respectively[12]. Although this study was limited by a relatively small sample size, the discovery of SWI/SNF complex genomic variants associated with PC susceptibility provides a good starting point for the development of markers to better-identify PC cases early-on, possibly saving many lives.

Finally, to address the relationship between SWI/SNF component expression and the clinical significance of pancreatic cancer, Numata et al. compared expression levels of SWI/SNF components with different clinicopathological features[4]. Using multivariate Cox proportional hazard analysis, expression levels of BRM and BAF180 were found to be significant independent predictors of overall survival in pancreatic cancer patients. The 5-year survival rate of low BRM patients was 43.8%, which was significantly higher than patients with high BRM expression (9.8%).

Furthermore, the 5-year survival rate of high BAF180 patients was 40.8%, which was significantly higher than patients with low BAF180 expression (8.1%)[4]. Knowing these relationships provides useful biomarkers for patients with curative resection.

Overall, SWI/SNF dysfunction has become increasingly characterized as playing a significant role in pancreatic cancer. While every individual subunit is not significantly mutated in a large proportion of cancers, the SWI/SNF complex is mutated in roughly one third of pancreatic cancers. Although much progress has occurred in recent years, the fundamental mechanisms by which SWI/SNF complexes drive tumorigenesis are not understood. The further characterization of the chromatin regulation role of SWI/SNF complexes and the functional pathways of SWI/SNF subunits can help to identify important targets for drug development to ameliorate pancreatic cancer and other cancer types.

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