

IRX4 plays an important role in pancreatic carcinogenesis

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学 位 論 文 要 約

博士論文題目 *IRX4* plays an important role in pancreatic carcinogenesis
(*IRX4* は膵の発がんで重要な役割を果たしている)

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Epigenetic gene silencing by aberrant DNA methylation is one of the important mechanisms leading to the loss of key cellular pathways in tumorigenesis. Methyl-CpG targeted transcriptional activation (MeTA) reactivates hypermethylation-mediated silenced genes in a different way from DNA demethylating agents. Previous pilot study using microarray coupled with MeTA (MeTA-array) identified seven commonly hypermethylation-mediated silenced genes in pancreatic cancer cell lines. In this study, *IRX4* (Iroquois homeobox 4) was focused on because this gene has recently been identified as a candidate tumor suppressor gene in prostate cancer. *IRX4* was greatly downregulated in all the analyzed pancreatic cancer cell lines by promoter hypermethylation. In addition, *IRX4* promoter region was found to be frequently and specifically hypermethylated in primary resected pancreatic cancers (15/22: 68%); corresponding normal pancreatic tissues were unmethylated. Tetracycline-associated *IRX4* inducible expression system was constructed and a pancreatic cancer cell line PK-1 was analyze for further functional investigation; induction of *IRX4* suppressed cell growth of PK-1. DNA methylation-mediated silencing of *IRX4* is suggested as a frequent event that may confer growth advantage on pancreatic cancer.

Keywords: DNA methylation; Epigenetic gene silencing; *IRX4*; MeTA; Methyl-CpG binding domain; NFκB transcriptional activation domain; Pancreatic cancer