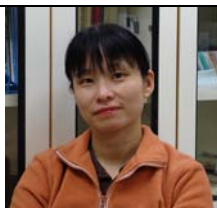


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101 學年：優良教師獎（醫學院基礎教學）

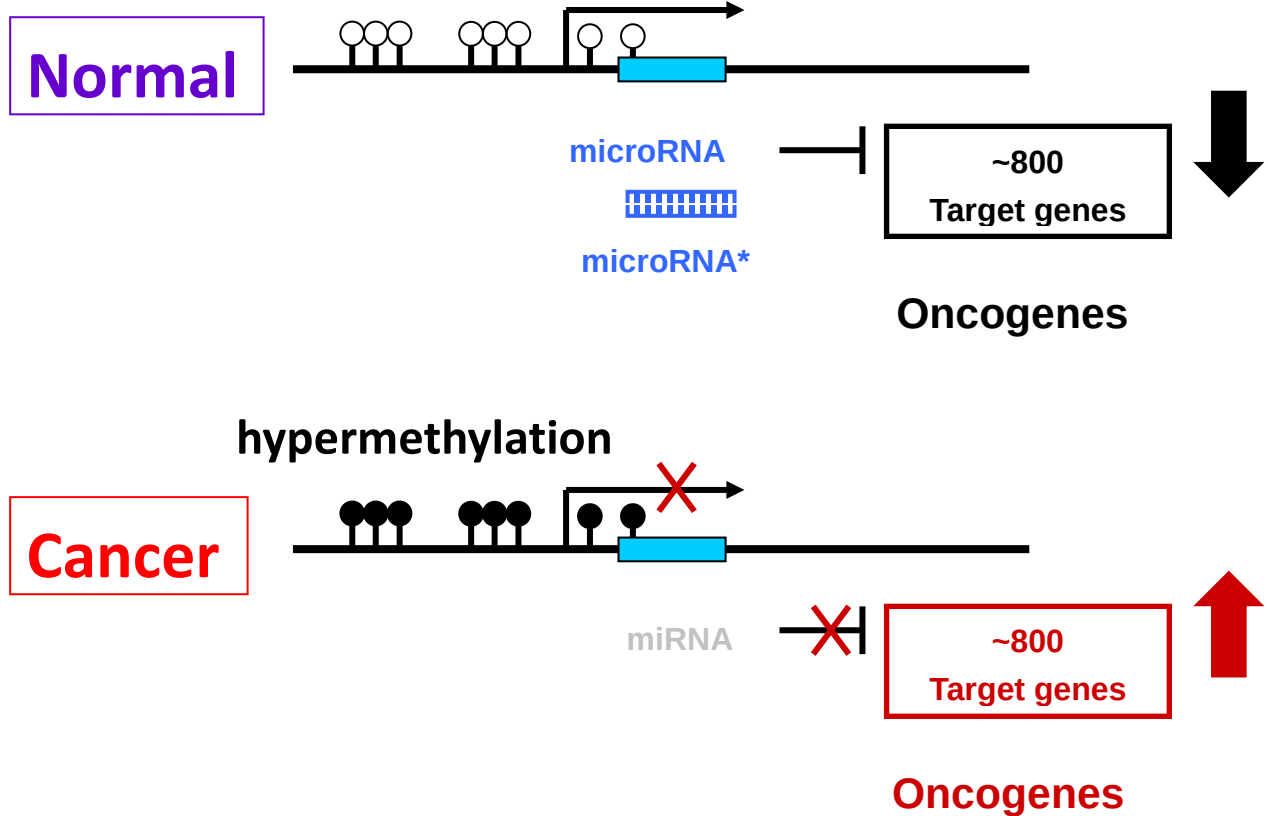
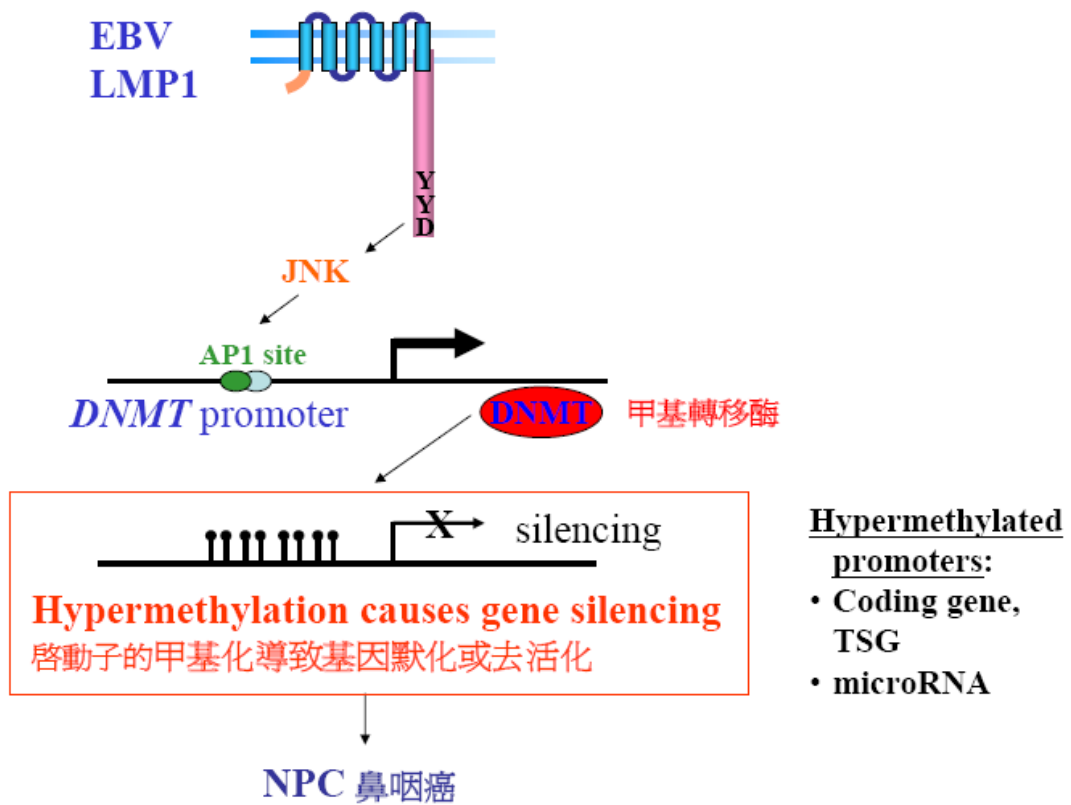
103 學年：優良教師獎（醫學院輔導類）

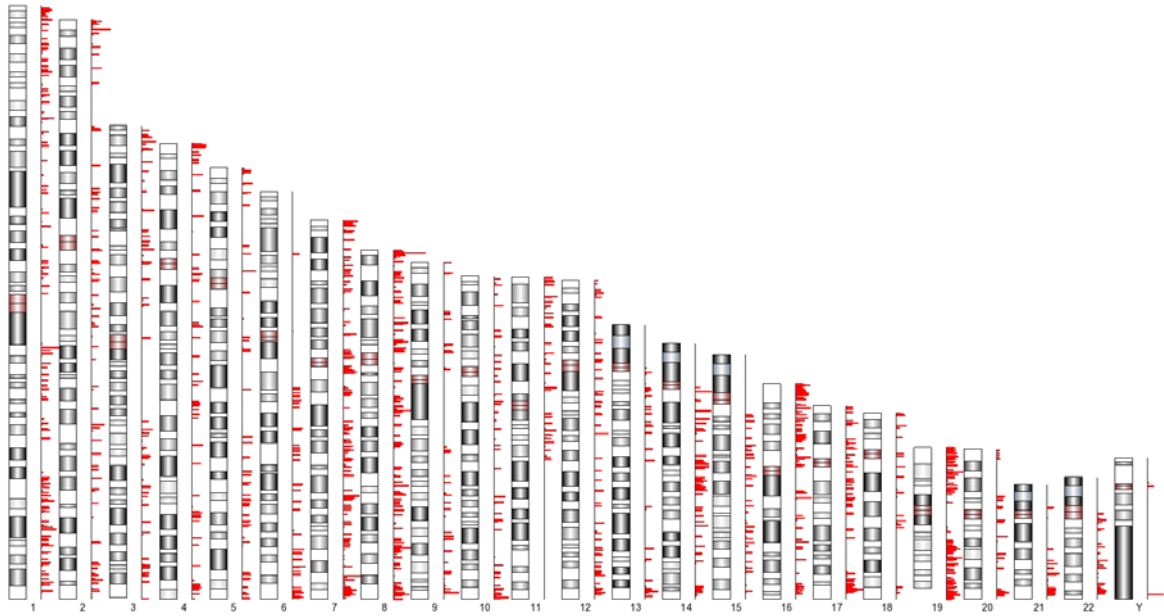
研究方向：

(1) 腫瘤病毒 EBV (2) 癌症研究 (3) DNA 甲基化

研究室特色 (2015/12)：

鼻咽癌(NPC)是與 EB 病毒密切相關的一種惡性腫瘤，好發於鼻咽鱗狀上皮細胞。在鼻咽癌檢體常發現有許多基因的缺失，其中包括“致癌基因”(Oncogenes)的活化以及“抑癌基因”(Tumor Suppressor Genes)的去活化。在腫瘤形成過程中，藉由“表觀遺傳”(Epigenetics)的修飾，如 DNA 甲基化 (DNA methylation)，可導致基因的去活化。我們曾報導在鼻咽癌組織中 EB 病毒的致癌基因”潛伏膜蛋白 1”(LMP1)，可活化細胞的 DNA 甲基轉移酶 (DNMT1)的表現，導致 DNA 過度甲基化，這可能跟鼻咽癌之致病機轉有密切關係。在癌細胞中，基因起動子區域之不正常甲基化，往往造成”抑癌基因”無法表現，進而促使癌症的發生。因此，DNMT1 的作用目標基因亦可被視為“抑癌基因”的候選基因。除了一般的基因，DNA 甲基化也同樣可抑制~22 核苷酸之微型核糖核酸(miRNA)基因的表現，由於每一種 miRNA 均具有調降 ~1000 mRNA 的產量，因此”抑癌-miRNA 基因”不正常的甲基化(抑癌-miRNA 可調降”致癌基因”的表現)，反而促進癌化的現象。本實驗室主要研究方向為(1)鑑別以及驗證在鼻咽癌細胞中潛在甲基化的差別”抑癌基因”及”miRNA 基因”；(2) 檢測鼻咽癌細胞株甲基化 miRNA 基因原來調控的目標 mRNA；(3)瞭解這些甲基化的抑癌基因及 miRNA 基因在鼻咽癌中的生理功能。

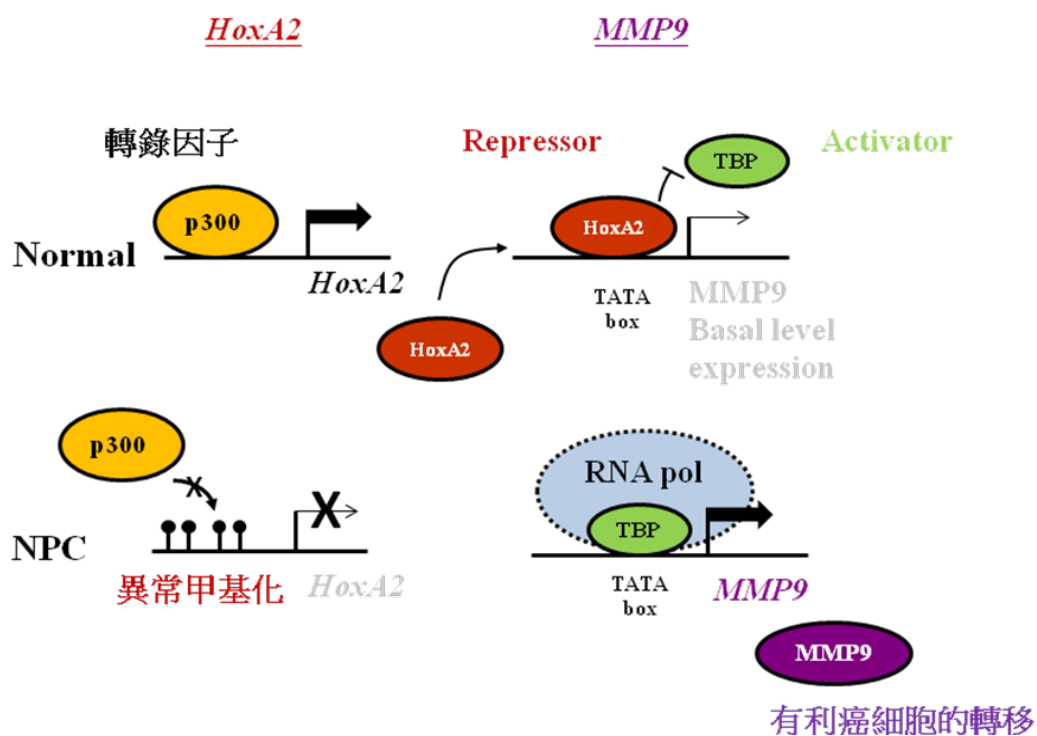




以免疫沈澱法ChIP-seq分離在鼻咽癌細胞株(C666.1)及正常鼻咽細胞株(NP69)甲基程度較高的DNA，並以定序方式分析及比較上述這兩種細胞株中甲基程度較高的DNA序列。其中鼻咽癌細胞株C666.1甲基化程度較高的DNA區域以紅線標示在23條染色體上。此圖顯示部分染色體的位置有明顯高度甲基化的情形，代表在鼻咽癌細胞中某此基因有可能受甲基化所影響，可進一步探討它們的基因表達是否受到抑制。

Aberrantly hypermethylated transcription repressor homeobox A2 derepresses metalloproteinase-9 activity through TBP and promotes invasion in nasopharyngeal carcinoma. (Oncotarget 2013; 4:2154-2165)

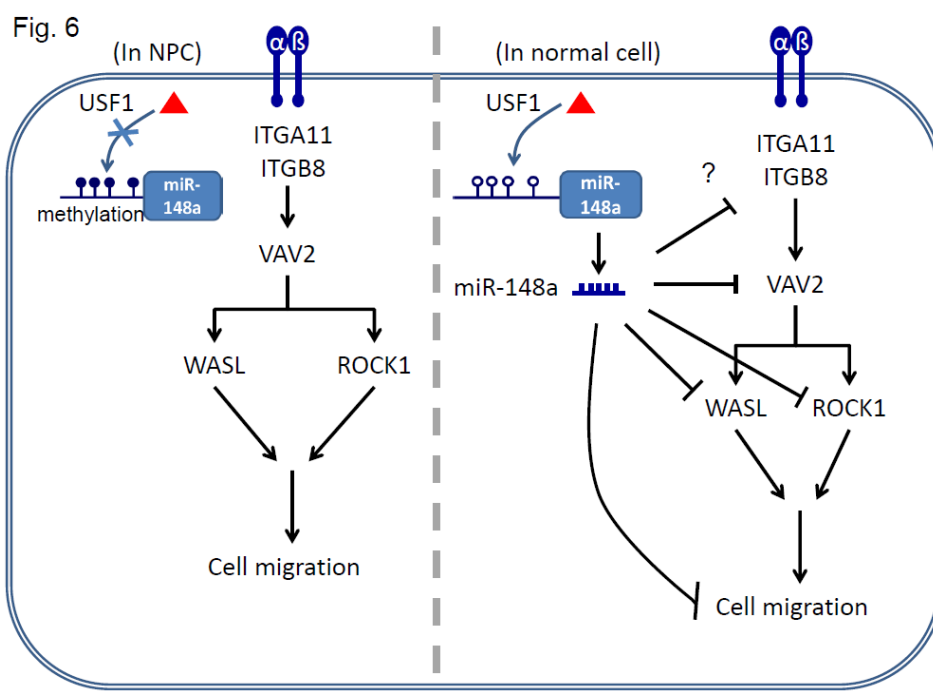
A differential hypermethylated transcription repressor, *Homeobox A2 (HOXA2)*, is identified in NPC tumor, which may render NPC cells invasive and metastatic. Aberrant hypermethylation of *HOXA2* led to low RNA expression in NPC tumors and cells. Addition of methylation inhibitor 5'aza restored *HOXA2* RNA expression in NPC cells. Methylated *HOXA2* promoter reduces the binding affinity of the transcriptional co-activator p300, causing transcriptional repression of *HOXA2*. In NPC cells, re-expression of ectopic *HOXA2* was correlated with decreased invasive ability and reduced metalloproteinase *MMP-9* RNA and protein expression. Promoter, ChIP and DNA-pull down assays indicated that *HOXA2* competes with the transcription activator, TATA-box binding protein (TBP) for a recognition sequence near the *MMP-9* transcription start site, and suppresses *MMP-9* transcription. Thus, *HOXA2* acts as a suppressor or TBP-antagonist to inhibit *MMP-9* expression; while methylation-mediated inactivation of *HOXA2* in NPC derepresses *MMP-9* production and increases invasion of NPC cells. In NPC plasma samples, increased plasma EBV copy number was correlated with increased in cell-free *HOXA2* hypermethylation and elevated *MMP-9* levels.



Oncotarget 2013; 4:2154-2165

Silencing of miR-148a by hypermethylation activates the integrin-mediated signaling pathway in nasopharyngeal carcinoma.
(Oncotarget 2014; (5)17:7610-24)

MiR-148a is downregulated through hypermethylation in NPC biopsies and NPC cell lines compared with adjacent normal and NP cells respectively. Promoter assays demonstrated that upstream stimulatory factor 1 (USF1) is a crucial transcription factor that activates miR-148a promoter activity. EMSA assays confirmed that purified USF1 binds better toward the unmethylated than the methylated CG-containing USF1 consensus probe. The ectopic expression of miR-148a inhibits cell migration in NPC cells through the suppression of integrin-mediated signaling by targeting VAV2, WASL and ROCK1. Furthermore, immunohistochemical staining and Western blotting analysis revealed that the 3 oncogenic targets of miR-148a were overexpressed in NPC biopsies, suggesting that the inactivation of miR-148a caused by DNA methylation promotes NPC progression. Overall, our findings revealed that miR-148a can act as tumor suppressor miRNA for NPC.



Oncotarget 2014 July; (5)17:7610-24

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Application of a patient-derived xenograft model in cytolytic viral activation therapy for nasopharyngeal carcinoma

Oncotarget 2015 Sept., advanced online publication (IF=6.627; R/C= 17/203; ONCOLOGY)

Hsin-Pai Li[†], Hsin-Yi Huang[†], Yi-Ru Lai, Jing-Xuan Huang, Kai-Ping Chang, Chuen Hsueh and Yu-Sun Chang ([†]Co-first author; *Corresponding)

Silencing of miRNA-148a by hypermethylation activates the integrin-mediated signaling pathway in nasopharyngeal carcinoma

Oncotarget 2014 July; (5)17:7610-24 (IF=6.627; R/C= 17/203; ONCOLOGY)

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ChIPseek, a web-based analysis tool for ChIP data

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Matrix metalloproteinase 12 is induced by heterogeneous nuclear ribonucleoprotein K and promotes migration and invasion in nasopharyngeal carcinoma

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