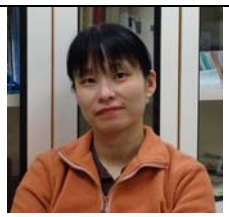
黎欣白(Hsin-Pai Li)

職稱：副教授	研究室名稱：腫瘤病毒及癌症研究	
最高學歷：Ph.D.	學校/國家：University of Southern California/ USA (Department of Microbiology)	
電話號碼：03-2118800 分機 #3593	電子郵件帳號： paili@mail.cgu.edu.tw	
實驗室：第一醫學大樓 7F Rm 0757		
研究室現有： 碩士生 4 人 大學生 2 人	博士班已畢業 2 人	碩士班已畢業 13 人
專任研究助理 2 人	大學部已指導專題生 22 人	



101 學年: 優良教師獎 (醫學院基礎教學)

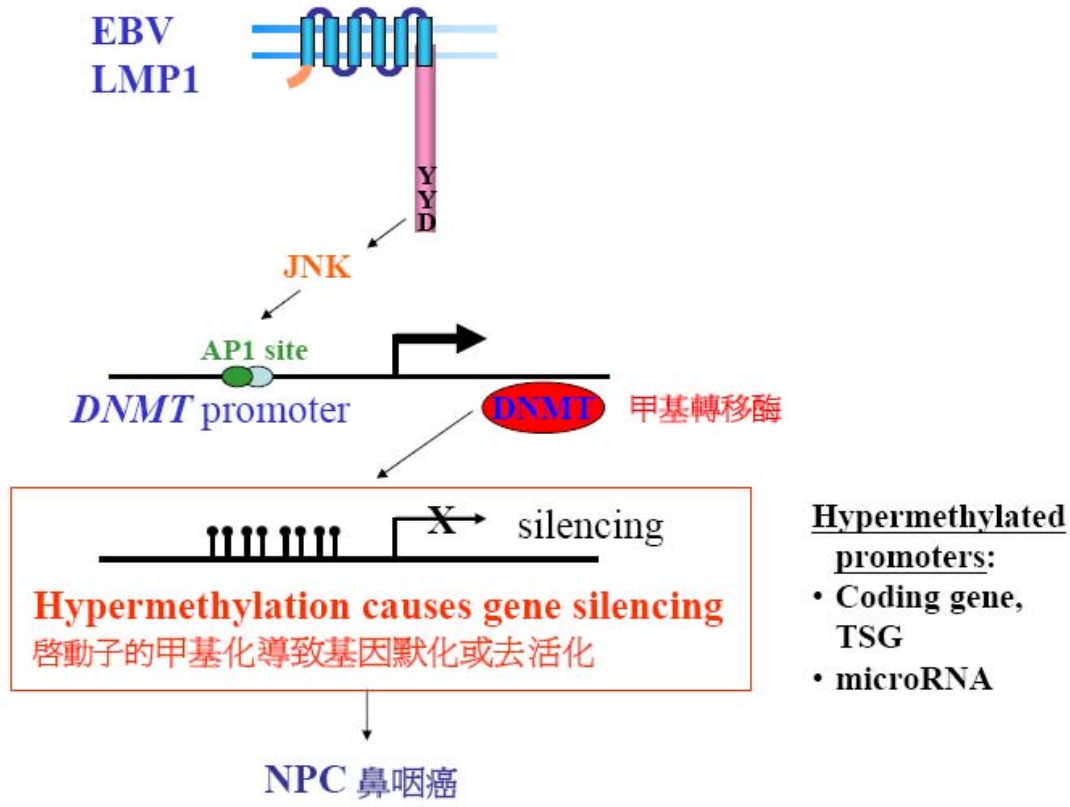
103 學年: 優良教師獎 (醫學院輔導類)

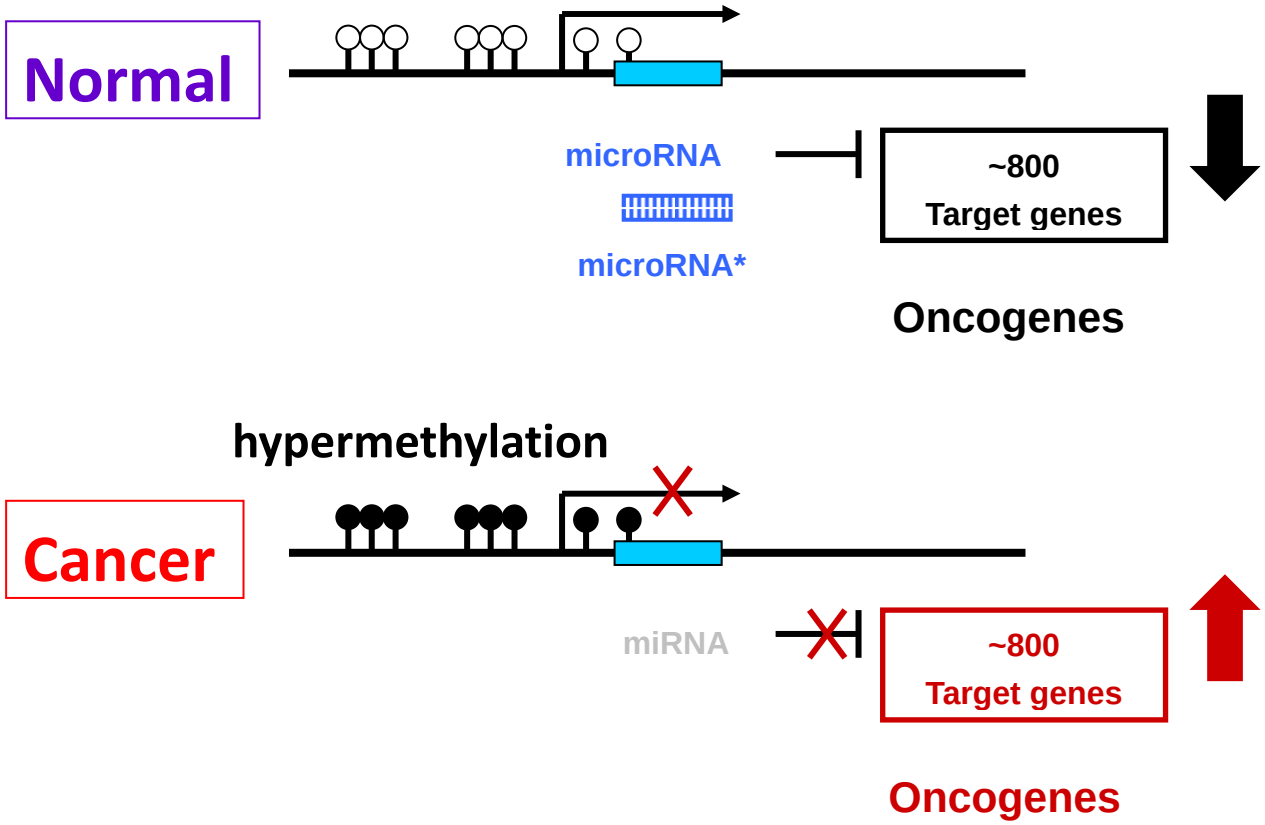
研究方向:

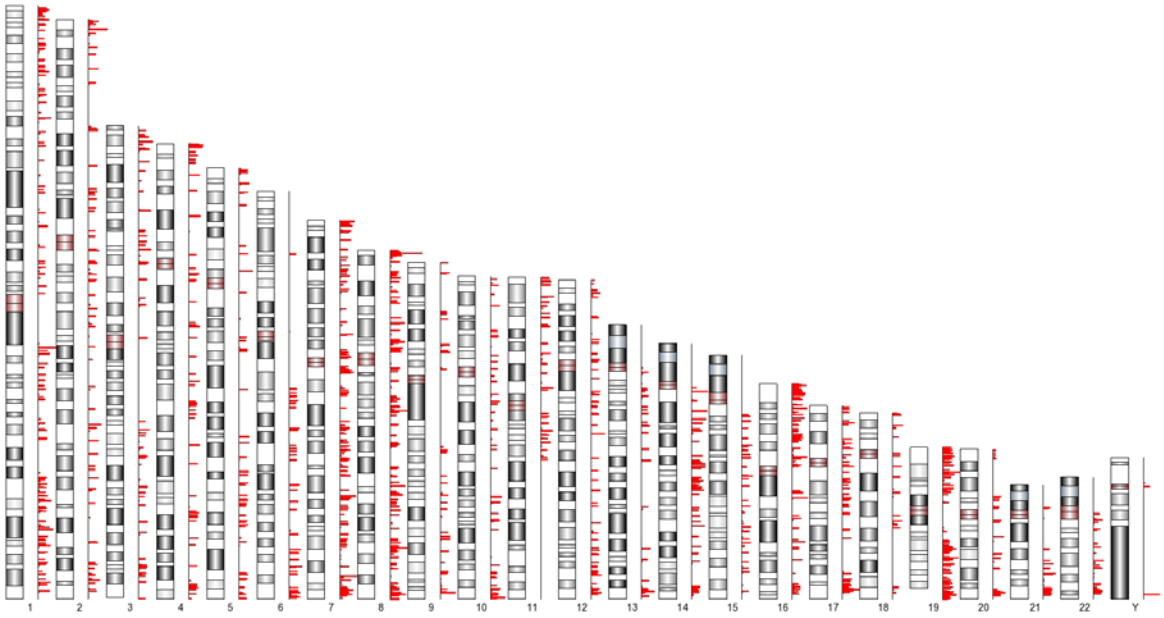
(1) 腫瘤病毒 EBV (2) 癌症研究 (3) DNA 甲基化

研究室特色 (2018/9)：

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 核苷酸之微型核醣核酸(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。


EBV
LMP1
YYD
JNK
AP1 site
DNMT promoter
DNMT
甲基轉移酶
X
silencing
Hypermethylation causes gene silencing
啓動子的甲基化導致基因默化或去活化
NPC 鼻咽癌
Hypermethylated promoters:
• Coding gene, TSG
• microRNA

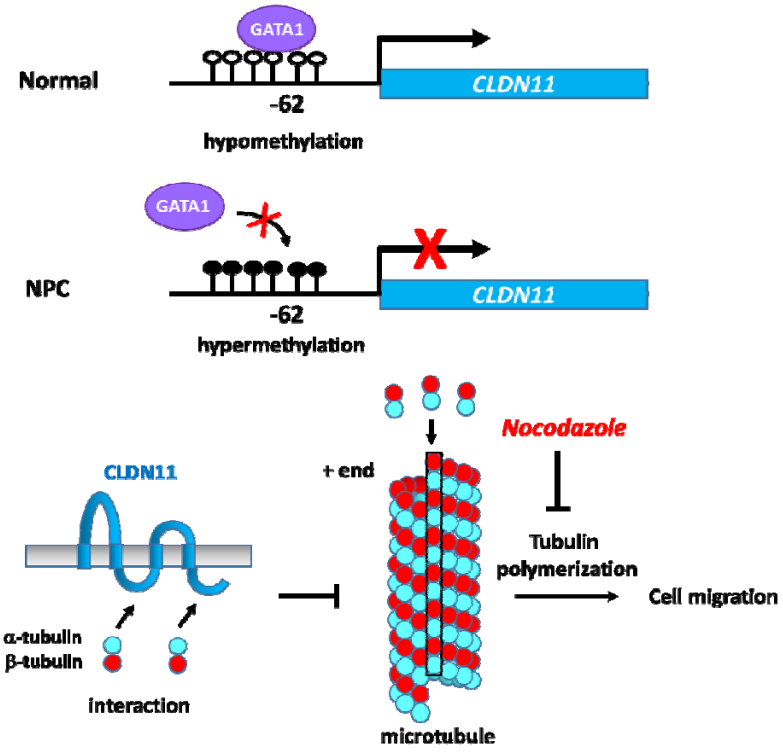

Normal
microRNA
microRNA*
~800
Target genes
Oncogenes
hypermethylation
Cancer
miRNA
~800
Target genes
Oncogenes



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。

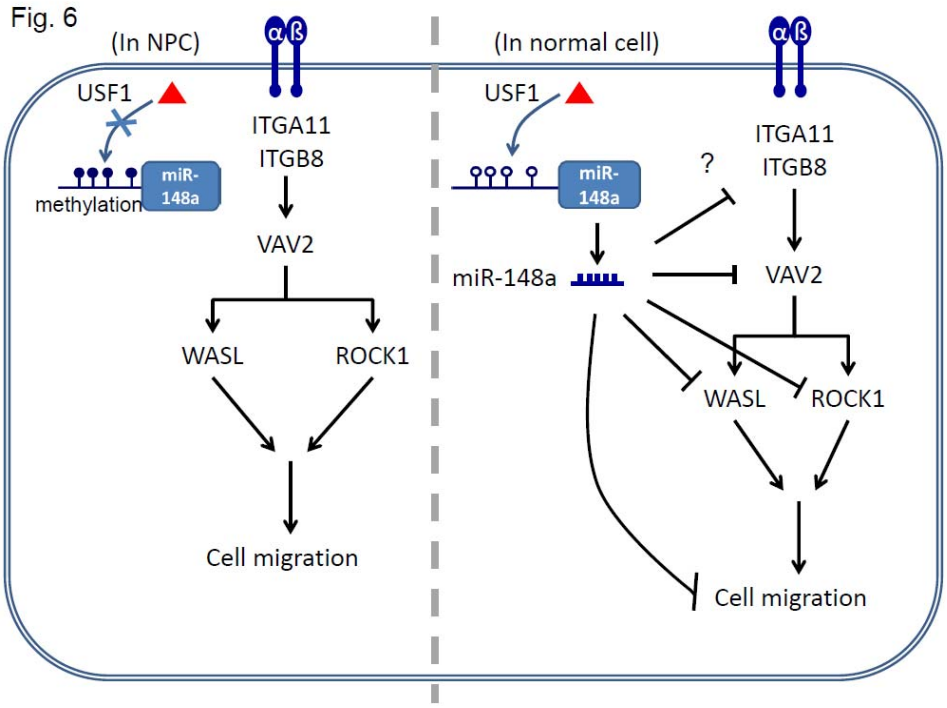
Inactivation of the tight junction gene CLDN11 by aberrant hypermethylation modulates tubulins polymerization and promotes cell migration in nasopharyngeal carcinoma (Journal of Experimental & Clinical Cancer Research 2018 37:102; IF=6.217)

We identified a differentially hypermethylated and downregulated tight junction gene, *CLDN11*, in NPC cells. The bisulfite sequencing of the *CLDN11* promoter and qRT-PCR of CLDN11 mRNA in seven paired NPC clinical samples indicated that methylation percentage of the promoter was conversely correlated with the mRNA expression level. Immunohistochemistry staining of independent NPC clinical samples demonstrated that the CLDN11 protein expression level decreased in seven of nine paired NPC tumor samples. Treatment with a DNA methylation inhibitor, 5'aza, restored CLDN11 RNA expression in NPC cell lines. *CLDN11* promoter deletion and site-directed mutation experiments suggested that the −62 to −53 region containing transcription activator GATA1 binding site is responsible for *CLDN11* activation. The re-expression of *CLDN11* inhibited cell migration and invasion abilities in NPC cells. Through co-immunoprecipitation and LC–MS/MS, we next identified the major components of microtubules, tubulin alpha-1b (TUBA1B) and beta-3 (TUBB3), are the novel CLDN11-interacting proteins. CLDN11 interacts with these two tubulins through its intracellular loop and C-terminus. More importantly these domains are required for CLDN11-mediated cell migration inhibition. The treatment with a tubulin polymerization inhibitor, nocodazole, blocked NPC cell migration. Collectively, our data provided insights that CLDN11 functions as a potential tumor suppressor gene and the inactivation of CLDN11 by DNA hypermethylation promotes NPC progression.



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

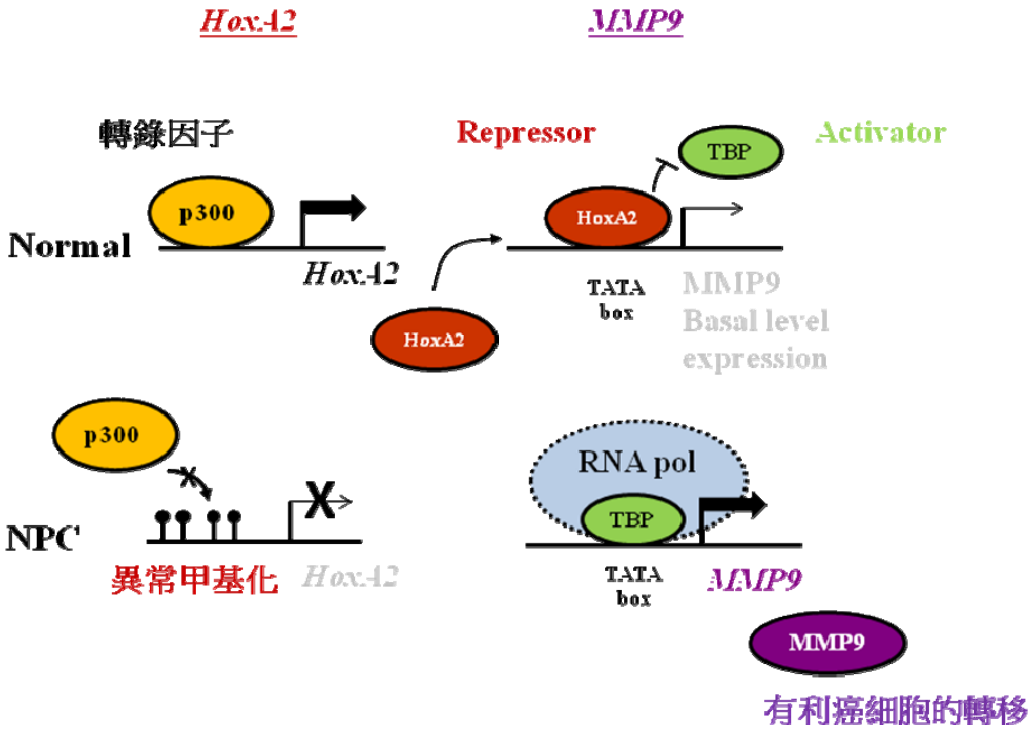
MiRNA-148a is downregulated through hypermethylation in NPC biopsies and NPC cell lines compared with adjacent normal and NP cells respectively. Promoter assays demonstrated that upstream stimulatory factor 1 (USF1) is a crucial transcription factor that activates miR-148a promoter activity. EMSA assays 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

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 metastaic. 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.



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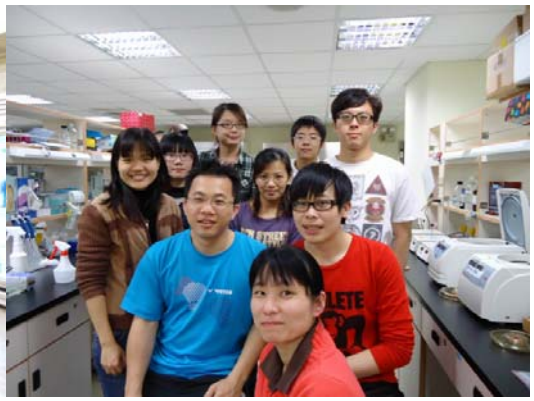
HPL Lab Photos







恭賀
裂欣白老師
榮獲醫學院基礎
科學類優良教師將
微免全體師生同賀
教不嚴師之情