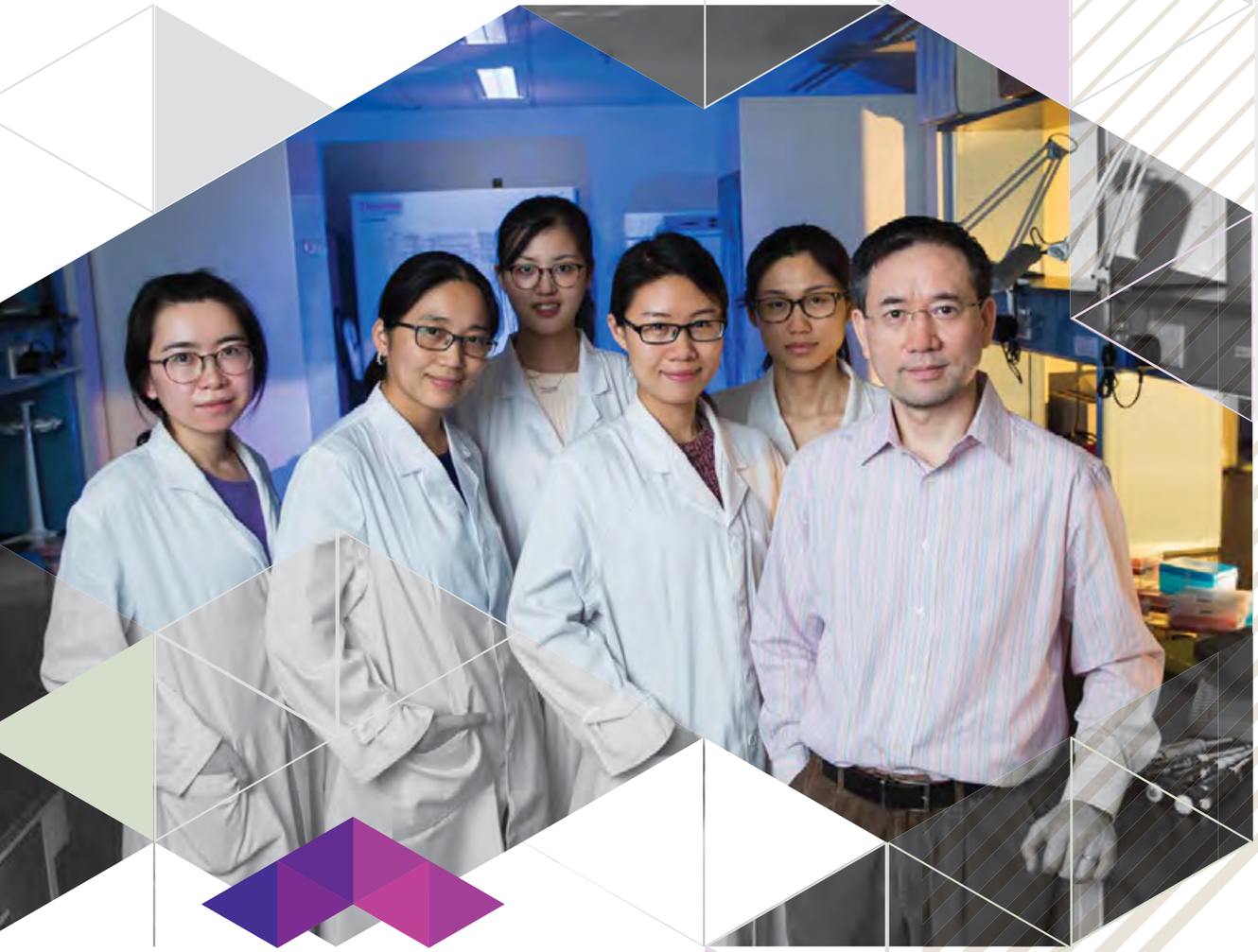
ASIAN CANCERS
(Cancer Epigenetics)



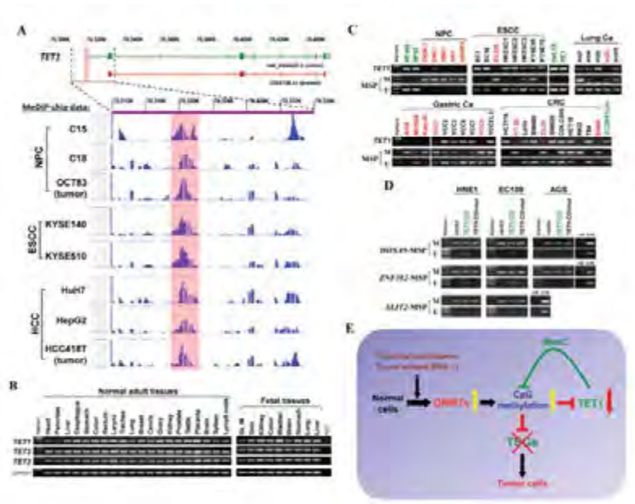
Principal Investigator

Professor Qian Tao

Research Progress Summary

Promoter CpG methylation is a fundamental regulatory process of gene expression. TET proteins are active CpG demethylases converting 5-methylcytosine to 5-hydroxymethylcytosine, with loss of 5 hmC as an epigenetic hallmark of cancers, indicating critical roles of TET proteins in epigenetic tumorigenesis. Through the analysis of tumour methylomes, Professor Qian Tao and his team discovered TET1 as a methylated target, and further confirmed its frequent downregulation / methylation in cell lines and primary tumours of multiple carcinomas and lymphomas, including nasopharyngeal, oesophageal, gastric, colorectal, renal, breast and cervical carcinomas, as well as non-Hodgkin, Hodgkin and nasal natural killer / T-cell lymphomas, though all three TET family genes are ubiquitously expressed in normal tissues. Ectopic expression of TET1 catalytic domain suppressed colony formation and induced apoptosis of tumour cells of multiple tissue types, supporting its role as a broad bona fide tumour suppressor. Furthermore, TET1 catalytic domain possessed demethylase activity in cancer cells, being able to inhibit the CpG methylation of tumour suppressor gene (TSG) promoters and reactivate their expression, such as SLIT2, ZNF382 and HOXA9. As only infrequent mutations of TET1 have been reported, compared to TET2, epigenetic silencing therefore appears to be the dominant mechanism for TET1 inactivation in cancers, which also forms a feedback loop of CpG methylation during tumorigenesis.

Through elucidating cancer methylome, the team found a series of newly identified, aberrantly methylated genes in lung, breast and renal cancers, such as CHD5, PAX5, DACT2 and PCDH17. They found that the epigenetic modifier CHD5 functions as a novel tumour suppressor for renal cell carcinoma and is predominantly inactivated by promoter CpG methylation; PAX5 is a frequently methylated lung cancer tumour suppressor gene interfering β-catenin signalling and GADD45G expression; DACT2 silencing by promoter CpG methylation disrupts its regulation of epithelial-to-mesenchymal transition and cytoskeleton reorganisation in breast cancer cells; PCDH17 functions as a tumour suppressor suppressing Wnt/β-catenin signalling and cell metastasis and is frequently methylated in breast cancer.



Characterisation of CpG methylation feedback loop mediated by DNMTs and TET1 during human tumorigenesis. When normal cells are exposed to carcinogens (chemical carcinogens, tumour viruses, etc.), DNA methyltransferases (DNMTs) are induced, upregulated or overactivated, which further generates higher levels of DNA CpG methylation (5 mC). Elevated level of 5 mC on tumour suppressor gene (TSG) promoters lead to TSGs silencing and functional inactivation, ultimately to tumorigenesis. Ten-eleven-translocation (TET) proteins catalyse DNA CpG demethylation through converting 5 mC to 5-hydroxymethylcytosine (5 hmC), maintaining a delicate balance between CpG methylation and demethylation in normal cells. While in premalignant or tumour cells, CpG demethylation by TET would induce TSG promoter demethylation and functional restoration for further tumour suppression. Thus unlike normal cells where TET proteins are abundant, loss of TET1 expression through promoter CpG methylation frequently occurs in tumour cells, which in turn, increases 5 mC levels and promotes TSG inactivation in tumour pathogenesis.

Recognitions

Awards and Fellowships

Member's Full Name	Details
Lili Li	2nd Prize, SYSU-Hong Kong Joint Report Poster Award, State Key Laboratory in Oncology in South China, 2016
Chen Li	2nd Prize, SYSU-Hong Kong Joint Report Poster Award, State Key Laboratory in Oncology in South China, 2016
Zhenfang Du	3rd Prize, SYSU-Hong Kong Joint Report Poster Award, State Key Laboratory in Oncology in South China, 2016

Grants and Consultancy

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Qian Tao	Mechanism Study of a New RhoA-signaling Antagonist in Esophageal Cancer Pathogenesis	The National Natural Science Foundation of China	01/2016	12/2019	RMB 570,000
Qian Tao (Co-PI)	Systematic Development of Molecular Targets for Nasopharyngeal Carcinoma	Research Grants Council - Theme-based Research Scheme	01/2014	12/2018	55,610,000

Publications

A. Journal Papers

1. Li L, Li C, Mao H, Du Z, Chan WY, Murray P, Luo B, Chan AT, Mok TS, Chan FK, Ambinder RF, Tao Q. Epigenetic inactivation of the CpG demethylase TET1 as a DNA methylation feedback loop in human cancers. *Scientific Reports.* 2016; 6:26591.
2. Du Z, Li L, Huang X, Jin J, Huang S, Zhang Q, Tao Q. The epigenetic modifier CHD5 functions as a novel tumor suppressor for renal cell carcinoma and is predominantly inactivated by promoter CpG methylation. *Oncotarget.* 2016; 7(16):21618-30.
3. Zhao L, Li S, Gan L, Li C, Qiu Z, Feng Y, Li J, Li L, Li C, Peng W, Xu C, Wang Z, Hui T, Ren G, Tao Q, Xiang T. Paired box 5 is a frequently methylated lung cancer tumour suppressor gene interfering β-catenin signalling and GADD45G expression. *Journal of Cellular and Molecular Medicine.* 2016; 20(5):842-54.
4. Xiang T, Fan Y, Li C, Li L, Ying Y, Mu J, Peng W, Feng Y, Oberst M, Kelly K, Ren G, Tao Q. DACT2 silencing by promoter CpG methylation disrupts its regulation of epithelial-to-mesenchymal transition and cytoskeleton reorganization in breast cancer cells. *Oncotarget.* 2016; 7(43):70924-35.
5. Yin X, Xiang T, Mu J, Mao H, Li L, Huang X, Li C, Feng Y, Luo X, Wei Y, Peng W, Ren G, Tao Q. Protocadherin 17 functions as a tumor suppressor suppressing Wnt/β-catenin signaling and cell metastasis and is frequently methylated in breast cancer. *Oncotarget.* 2016; 7(32):51720-32.

B. Conference Papers

1. Tao Q. Cancer epigenomics identified the epigenetic inactivation of CpG demethylase TET1 as a DNA methylation feedback loop in multiple human cancers. In: *The 5th international cancer epigenetics meeting*; Beijing, China; 2016 Oct 20-24.
2. Tao Q. In: *The 7th Sino-France International Breast Cancer Forum*; Chongqing, China; 2016 Apr 14-17.
3. Li L, Li C, Mao H, Du Z, Murray P, Chan AT, Ambinder RF, Tao Q. A DNA methylation feedback loop through epigenetic inactivation of the CpG demethylase TET1 is involved in NPC pathogenesis. In: *Nasopharyngeal Carcinoma - Gordon Research Conference*; Hong Kong; 2016 Jun 26 - Jul 1.