03
ASIAN CANCERS
(Integrated Genome Research)

Principal Investigators

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Research Progress Summary

In this year, the research group led by Professor Ka-fai To, Professor Kwok-wai Lo and Professor Nathalie Wong have completed a nasopharyngeal cancer (NPC) genomics study on a large cohort of 111 microdissected EBV-associated NPC tumours. By whole exome and whole genome sequencing, they established a precise genome landscape of this "Cantonese Cancer". In addition to the reported 5-methyl-cytosine deamination signature, their study firstly revealed a predominant defective DNA mismatch repair signature in NPC, suggesting the contribution of inactivation of mismatch repair mechanism in tumour development. By integrated informatics and functional analysis, they have identified the significant mutated genes and potential drivers in this EBV-associated epithelial cancer. Strikingly, the team discovered the high frequencies of somatic alterations (41%) in multiple negative regulators of NF-κB signalling pathways (e.g. CYLD, TRAF3, NFKBIA, NLRC5). The integrated analysis revealed a mutually exclusive relationship among somatic NF-κB pathway aberrations and overexpression of LMP1 in NPC. The novel findings strongly implicate the importance of NF-κB activation in NPC pathogenesis either by constitutive activation through somatic mutations or activated by the EBV-encoded oncoprotein, LMP1. The new genomic information has been summarised in a new NPC tumorigenesis models in an invited review (Philosophical Transactions B, 2017). Importantly, the NPC genome study has systematically identified a number of new biomarkers and molecular targets for developing novel therapeutic strategies for NPC patients. In this study, they demonstrated how NPC genomics can potentially inform therapy, highlighting the importance of targeting activated NF-κB signalling in NPC patients with somatic defects in NF-κB negative regulators. Furthermore, the team also firstly revealed the association of increasing mutational burden and mutations of MHC class I molecules with poor clinical outcome of the patients. The discovery of MHC Class I lesions in a subgroup of NPC (30%) is believed to have biological implications for immune checkpoint inhibitors or other cytotoxic T cell-based immunotherapies in NPC. Aside from genome landscape, they also established a comprehensive EBV transcriptome in NPC. The viral transcriptome map unveiled novel EBV transcripts and abundance expressed latent genes which interfere critical cellular mechanisms during NPC tumorigenesis. Among EBV-encoded latent genes, a group of predominantly expressed EBV-encoded miR-BARTs were found in EBV-associated NPC. Multiple abundantly expressed miR-BARTs (BART5-5p, BART7-3p, BART9-3p and BART14-3p) were shown to be able to negatively regulate the expression of a key DNA double-strand breaks (DSBs) repair gene, ATM, thereby controlling DNA damage repairs and inhibiting EBV lytic reactivation. The discovery unveiled the potential roles of EBV infection in enhancing the sensitivity of NPC cells to radio- and chemotherapies.

In the research of hepatocellular carcinoma (HCC), the team analysed Viral Hepatitis B (HBV) and Non-Alcoholic Steatohepatitis (NASH) associated HCC for the mutation spectrum and showed shared and common mutagenic signatures. Using the logarithm of Nonnegative Matrix Factorization (NMF), the team identified 4 signatures of different strengths in NASH and HBV associated tumours, namely Signatures 1b, 4, 12, and 16. Despite there is an overall predominance of Signature 1B in both NASH and HBV, they were able to identify changes in contribution of these extracted signatures. The team found significantly simpler contribution of signatures in NASH compared to HBV cases (P=0.042). Interestingly, NASH-HCC also showed a significantly lower contribution of Signature 16 (P=0.0214) and higher Signature 4. Although Signatures 1B and 4 have been implicated in bulky DNA adducts, factors affecting Signatures 12 and 16 remain unknown. Given the strong association of these 2 signatures with transcriptional strand bias, it is possible that Signatures 12 and 16 may be associated with transcription-coupled nucleotide excision repair. Functional clustering of SNVs in HBV- and NASH- associated HCC also revealed deregulated pathways that were previously not emphasised in NASH-HCC, including Notch signalling: NASH=35.29% vs HBV=15.38% and Foxo pathway: NASH=52.94% vs HBV=23.08%. In addition, recurring SNVs involved in Hedgehog signalling (such as LRP2 and BOC) were also found. These findings hold potential therapeutic implications for NASH-HCC as Notch and Hh are druggable targets (e.g. γ-secreatase inhibitors in clinical trials for targeting Notch, and Vismodegib, an FDA approved drug for Hh inhibition).

Recognitions

Grants and Consultancy

Full Name of PI	Project Title	Funding Source	Start Date (dd/mm/yyyy)	End Date (dd/mm/yyyy)	Amount (HK$)
Ka-fai To	Target Inhibition of ATM-Mediated Homologous Recombination Repair by Epstein-Barr Virus miR-BARTs in Nasopharyngeal Carcinoma: Molecular Mechanisms and Clinical Implications	Research Grants Council – General Research Fund	01/09/2016	31/08/2018	811,383
Ka-fai To (Co-PI)	Functional Liver Cancer Epigenomics: Exploiting Epigenetic Vulnerabilities for Therapeutics	Research Grants Council – Collaborative Research Fund	01/06/2015	31/05/2018	7,418,375
Nathalie Wong (Co-PI)	Functional Liver Cancer Epigenomics: Exploiting Epigenetic Vulnerabilities for Therapeutics	Research Grants Council – Collaborative Research Fund	01/06/2015	31/05/2018	7,418,375
Nathalie Wong (Co-I)	Establishment of Third Generation Sequencing Core Facility	Research Grants Council – Collaborative Research Fund Equipment Grant	01/06/2017	31/05/2020	3,222,257

Publications

A. Journal Papers

1. Li YY, Chung GT, Lui VW, TO KF, Ma BB, Chow C, Woo JK, Yip KY, Seo JS, Hui EP, Mak MK, Rusan M, Chau NG, Or YY, Law MH, Law PP, Liu ZW, Ngan HL, Hau PM, Verhoeft KR, Poon PH, Yoo SK, Shin JY, Lee SD, Lun SW, Jia L, Chan AW, Chan JY, Lai PB, Fung CY, Hung ST, Wang L, Chang AM, Chiosea SI, Hedberg ML, Tsao SW, van Hasselt AC, Chan AT, Grandis JR, Hammerman PS, Lo KW. Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations. *Nature Communications*. 2017; 8:14121.
2. Xu M, Cheung CC, Chow C, Lun SW, Cheung ST, Lo KW. Overexpression of PIN1 enhances cancer growth and aggressiveness with Cyclin D1 induction in EBV-associated nasopharyngeal carcinoma. *PLOS One*. 2016; 11(6):e0156833.
3. Cheung CC, Lun SW, Chung GT, Chow C, Lo C, Choy KW, Lo KW. MicroRNA-183 suppresses cancer stem-like cell properties in EBV-associated nasopharyngeal carcinoma. *BMC Cancer*. 2016; 16:495.
4. Huang T, Zhou Y, Cheng AS, Yu J, To KF, Kang W. NOTCH receptors in gastric and other gastrointestinal cancers: oncogenes or tumor suppressors? *Molecular Cancer*. 2016; 15(1):80.
5. Chan AW, Chong CC, Mo FK, Wong J, Yeo W, Johnson PJ, Yu S, Lai PB, Chan AT, To KF, Chan SL. Applicability of albumin-bilirubin-based Japan integrated staging score in hepatitis B-associated hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology*. 2016; 31(10):1766-72.
6. Chan AW, Yu S, Yu YH, Tong JH, Wang L, Tin EK, Chong CC, Chan SL, Wong GL, Wong VW, Chan HL, Lai PB, To KF. Steatotic hepatocellular carcinoma: a variant associated with metabolic factors and late tumour relapse. *Histopathology*. 2016; 69(6):971-84.
7. Kang W, Cheng AS, Yu J, To KF. Emerging role of Hippo pathway in gastric and other gastrointestinal cancers. *World Journal of Gastroenterology*. 2016; 22(3):1279-88. (Review)
8. Zhou Y, Huang T, Cheng AS, Yu J, Kang W, To KF. The TEAD Family and its oncogenic role in promoting tumorigenesis. *International Journal of Molecular Sciences*. 2016; 17(1):138. (Review)
9. Huang T, Kang W, Zhang B, Wu F, Dong Y, Tong JH, Yang W, Zhou Y, Zhang L, Cheng AS, Yu J, To KF. miR-508-3p concordantly silences NFKB1 and RELA to inactivate canonical NF-κB signaling in gastric carcinogenesis. *Molecular Cancer*. 2016; 15:9.
10. Chan AW, Kumada T, Toyoda H, Tada T, Chong CC, Mo FK, Yeo W, Johnson PJ, Lai PB, Chan AT, To KF, Chan SL. Integration of albumin-bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology*. 2016; 31(7):1300-6.
11. Wang S, Meng XM, Ng YY, Ma FY, Zhou S, Zhang Y, Yang C, Huang XR, Xiao J, Wang YY, Ka SM, Tang YJ, Chung AC, To KF, Nikolic-Paterson DJ, Lan HY. TGF-β/Smad3 signalling regulates the transition of bone marrow-derived macrophages into myofibroblasts during tissue fibrosis. *Oncotarget*. 2016; 7(8):8809-22.

B. Conference Papers

1. Hau PM, Chung G, Lung R, Lung S, Chow C, Wong A, Liu FF, Tsao G, Yip K, To KF, Lo KW. The identification of UBR5-ZNF423 recurrent fusion gene in EBV-associated nasopharyngeal carcinoma. In: *2016 AACR Annual meeting*; New Orleans, USA; 2016 Apr 16-20.
2. Lung RWM, Hau TPM, Chak WP, Tong JHM, Yu KHO, Tsao SW, Yip KYL, To KF, Lo KW. The role of Epstein-Barr virus-encoded mRNAs in ATM regulating DNA damage response in nasopharyngeal carcinoma. In: *2016 AACR Annual meeting*; New Orleans, USA; 2016 Apr 16-20.
3. Lo KW, Li YY, Chung GT, Lui VW, To KF, Ma BB, Woo JK, Grandis JR, Hammerman PS. Whole exome and genome sequencing identifies frequent NF-κB pathway activating mutations in EBV-associated nasopharyngeal carcinoma. In: *17th International Symposium on Epstein-Barr virus and associated diseases*; Zurich, Switzerland; 2016 Aug 8-12.