Asian Cancers (Integrated Genome Research)

Principal Investigators
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Professor Nathalie Wong

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 model 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 drugable targets (e.g. γ-secretase inhibitors in clinical trials for targeting Notch, and Vismodegib, an FDA approved drug for Hh inhibition).
Appendix: Asian Cancers
LI KA SHING INSTITUTE OF HEALTH SCIENCES PROGRESS REPORT 2016

Recognitions
Grants and Consultancy

<table>
<thead>
<tr>
<th>Full Name of PI</th>
<th>Project Title</th>
<th>Funding Source</th>
<th>Start Date (dd/mm/yyyy)</th>
<th>End Date (dd/mm/yyyy)</th>
<th>Amount (HK$)</th>
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<td>Ka-fai To</td>
<td>Target Inhibition of ATM-Mediated Homologous Recombination Repair by Epstein-Barr Virus miR-BARTs in Nasopharyngeal Carcinoma: Molecular Mechanisms and Clinical Implications</td>
<td>Research Grants Council – General Research Fund</td>
<td>01/09/2016</td>
<td>31/08/2018</td>
<td>811,383</td>
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| Ka-fai To (Co-PI) | Functional Liver Cancer Epigenomics: Exploring 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: Exploring 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


B. Conference Papers

