Lee-Jun C. Wong, Ph.D.

Professor of Molecular and Human Genetics

Other Positions

Director, Mitochondrial Laboratory, BCM Medical Genetics Laboratories

Professor, Program in Translational Biology & Molecular Medicine

Education

B.S., National Taiwan University, 1971
Ph.D., Ohio State University, 1975
Postdoc, Princeton University, 1976

Research Interests

My primary research interest is in the understanding of mitochondrial genetics and function in disease, cancer, and aging. For many years our laboratory has had its major contribution to the improvement of the molecular diagnosis of the very complex dual genome mitochondrial disorders. This includes the development of mutation detection methods, a one-step real time quantitative PCR technique for the detection and quantification of heteroplasmic mtDNA mutations, sequence analyses of mitochondrial and nuclear genes, as well as simultaneous detection of copy number changes in these two genomes, including mtDNA deletions and mtDNA depletion, using oligonucleotide array CGH (MitoMet array). Since the majority of the mitochondrial disorders are caused by nuclear gene defects, using novel massively parallel sequencing technique, we have developed a one-step comprehensive analysis of a group of mitochondrial targeted nuclear genes, allowing simultaneous analysis of point mutations and deletions of all genes related to mitochondrial disorders qualitatively and quantitatively.

Reprogramming of energy metabolism is one of the hallmarks of cancer. In proliferating cancer cells, the rates of glycolysis, lactate production, and biosynthesis of lipids and other macromolecules are increased. This Warburg effect is attributed to defective mitochondrial oxidative phosphorylation in cancer cells. Direct evidence for the role of bioenergetics in cancer comes from the occurrence of pathogenic mutations in energy metabolic genes, such as succinate dehydrogenase (SDH), a component (complex II) of the mitochondrial respiratory chain, which acts as a tumor suppressor and an oxygen sensor. In the past decade, numerous somatic mitochondrial DNA (mtDNA) alterations have been identified in almost all types of cancers. However, the functional significance of these mtDNA alterations in tumorigenesis is not clear. My research interest is to investigate the mechanism of interplay between the nuclear and mitochondrial genomes and to identify key modulators in the dual genome cross-talk that impact cellular energetics. Our hypothesis is that altered cancer mitochondria can transmit tumorigenic properties that modulate nuclear gene expression through key regulators in energy metabolic pathways and pathways involved in tumor development. Thus, the research activities in my laboratory include the establishment of transmitochondrial cybrids with a non-cancer background containing mitochondria derived from cancer cell lines with various degrees of tumorigenicity and metastatic potency. We will investigate the functional effect of cancer mitochondria by gene expression profiling to identify nuclear gene targets. Elucidation of how cancerous mitochondria regulate nuclear gene expression will provide insight into the mechanism of mitochondrial-nuclear cross-talk and the relationship between energy metabolism and cancer development.

Germline mtDNA variations and haplogroups may be modifying factors for cancer predisposition and/or metabolic syndromes. We have genotyped 78 mtDNA variants in patients with breast cancer and healthy individuals. The results of haplogroup analyses showed that individuals with haplogroup K demonstrated a significant increase in the risk of breast cancer; whereas, individuals bearing haplogroup U had a significant decrease in the risk of breast cancer. Furthermore, some individual variations showed a significant protective effect; while others showed significant increase in breast cancer risk. Thus, our results suggest that mitochondrial DNA haplotypes and variants play a role in modifying an individual's risk to breast cancer. With the next generation sequencing technique, the whole mitochondrial genome of a large number of samples can be easily sequenced. The study of predisposition of mitochondrial genotype to common diseases is not only simplified but also cost effective.

Selected Publications

1. Tang S, Wang J, Lee NC, Milone M, Li Y, Halberg M, Schmitt ES, Craigen WJ, Zhang W, Wong LJ (2011). Mitochondrial DNA polymerase gamma mutations: an ever expanding molecular and clinical spectrum. *J. Med. Genet.* 48(10): 669-81. PubMed PMID: 21880868
2. Milone M, Wang J, Liewluck T, Chen LC, Leavitt JA, Wong LJ (2011). Novel *POLG* splice site mutation and optic atrophy. *Arch. Neurol.* 68(6): 806-11. PubMed PMID: 21670405
3. Tu YF, Kaipparettu BA, Ma Y, Wong LJ (2011). Mitochondria of highly metastatic breast cancer cell line MDA-MB-231 exhibits increased autophagic properties. *Biochim. Biophys. Acta* 1807(9): 1125-32. PubMed PMID: 21570379
4. Young MJ, Longley MJ, Li FY, Kasiviswanathan R, Wong LJ, Copeland WC (2011). Biochemical analysis of human *POLG2* variants associated with mitochondrial disease. *Hum. Mol. Genet.* 20(15): 3052-66. PubMed PMID: 21555342
5. Wang J, Shchelochkov OA, Zhan H, Li F, Chen LC, Brundage EK, Pursley AN, Schmitt ES, Häberle J, Wong LJ (2011). Molecular characterization of *CPS1* deletions by array CGH. *Mol. Genet. Metab.* 102(1): 103-6. PubMed PMID: 20855223
6. Compton AG, Troedson C, Wilson M, Procopis PG, Li FY, Brundage EK, Yamazaki T, Thorburn DR, Wong LJ (2011). Application of oligonucleotide array CGH in the detection of a large intragenic deletion in *POLG* associated with Alpers Syndrome. *Mitochondrion* 11(1): 104-7. PubMed PMID: 20708716
7. Sadikovic B, Wang J, El-Hattab A, Landsverk M, Douglas G, Brundage EK, Craigen WJ, Schmitt ES, Wong LJ (2010). Sequence homology at the breakpoint and clinical phenotype of mitochondrial DNA deletion syndromes. *PLoS One* 5(12): e15687. PubMed PMID: 21187929
8. Wong LJ (2010). Molecular genetics of mitochondrial disorders. *Dev. Disabil. Res. Rev.* 16(2): 154-62. PubMed PMID: 20818730
9. Dimmock D, Tang LY, Schmitt ES, Wong LJ (2010). Quantitative evaluation of the mitochondrial DNA depletion syndrome. *Clin. Chem.* 56(7): 1119-27. PubMed PMID: 20448188
10. Sansanwal P, Yen B, Gahl WA, Ma Y, Ying L, Wong LJ, Sarwal MM (2010). Mitochondrial autophagy promotes cellular injury in nephropathic cystinosis. *J. Am. Soc. Nephrol.* 21(2): 272-83. PubMed PMID: 19959713
11. Chinault AC, Shaw CA, Brundage EK, Tang LY, Wong LJ (2009). Application of dual genome oligonucleotide aCGH to the molecular diagnosis of mitochondrial DNA deletion and depletion syndromes. *Genet. Med.* 11(7): 518-26. PubMed PMID: 19546809

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