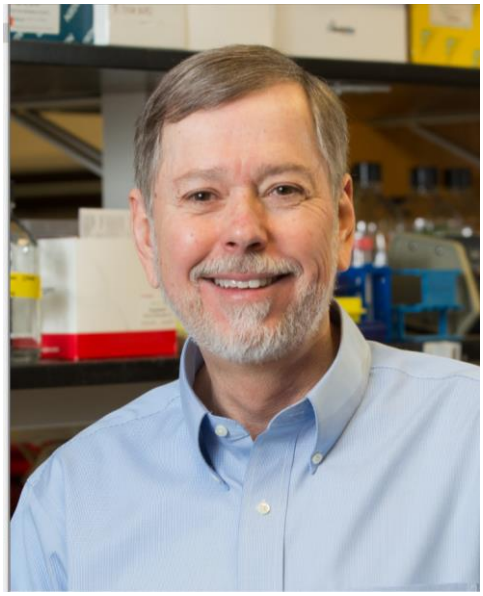
GUEST SPEAKER SEMINAR

Molecular Genetics
UNIVERSITY OF TORONTO

CNVs and common fragile sites: different outcomes of replication-transcription conflicts in highly unstable large genes



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Copy number variants (CNVs) are genomic deletions and duplications that contribute extensively to human genetic variation and disease but for which the mechanisms responsible for their formation are poorly understood. We found that partial inhibition of DNA replication (replication stress) by aphidicolin, hydroxyurea or other agents induces a high frequency of CNVs in cultured normal human cells that mimic non-recurrent CNVs found in humans. While they occurred throughout the genome, there are hotspots associated with large gene that are more prone to CNV formation. We found a high correlation among the genomic locations of CNV hotspots, large active transcription units and common fragile sites (CFSs), suggesting that active transcription of large genes contributes to both CFSs and CNVs instability at highly unstable loci. Unlike most transcribed genes, these large transcription units replicate late in the cell cycle. However, the majority of late-replicating regions are not CNV hotspots indicating that late replication alone is insufficient for CNV or CFS formation, and it is replication-transcription conflicts in large genes that drives this this process. Moreover, experimentally blocking their transcription eliminates instability at these loci. Thus, CFSs and CNVs are different outcomes of genome instability in large transcribed genes following replication stress. These observations allow us to predict locations of CFSs and CNV hotspots in any cell type with known transcription profiles including in cancers and in cells of the brain where many of the largest human genes have their primary function.

Hosts: Dr. Christopher Pearson

Date: Thursday, December 12th, 2019
Time: 2:00 PM
Place: PGCRL 3rd floor Multimedia Room