Department of Molecular and Cellular Biology

Graduate Seminar MCB*6500

Friday, March 9, 2018 in SSC 1511 @ 12:45 p.m.

presented by:

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(Advisor: M. Baker)

"Investigating Rad51 reduction in cells harbouring truncated human BRCA2 and its effects on homology directed DNA repair"

BRCA2 and Rad51 are two key protein partners involved in the homology directed repair (HDR) pathway that works to correct double stranded breaks in DNA, which is the most deleterious form of DNA damage. Key functional domains in human BRCA2 include a nuclear localization signal (NLS) within the C-terminus, upstream of which are eight highly conserved BRC repeats that interact with Rad51. Germline mutations in BRCA2 are associated with an increased risk of developing early onset breast and ovarian cancer. One aggressive allele, delT6174, produces a BRCA2 protein truncated within the seventh BRC repeat that is trapped within the cytosol. The current model suggests that Rad51 is sequestered from the nucleus by interacting with cytosolic BRCA2 and results in tumorigenesis. The Baker lab has observed that Rad51 protein levels are reduced in hybridoma cells containing hBRCA2 delT6174, suggesting an alternative mechanism. We hypothesize that truncated BRCA2 interacting with Rad51 in a cytosolic context generates a stress signal that promotes Rad51 degradation, which we will investigate by generating hybridoma cell lines expressing maltose binding protein tagged BRCA2 mutants truncated just before the BRC repeats, and after the fourth, sixth and eighth repeats. We will evaluate their impacts on Rad51 protein levels, cell growth, measure the efficiency of HDR, and determine if Rad51 reduction is a result of proteasomal degradation. Only by gaining a deeper understanding of the molecular mechanisms that drive tumorigenesis, can we identify drug targets that can help treat BRCA2 deficient cancers and mediate the risks for mutation carriers.