

## グローバルCOE セミナーのご案内

Date: October 30th, 2009

日時：平成21年10月30日（金）17:30～18:30

場所：医学部 A棟 103+107

講師：Professor Ashok Venkitaraman

University of Cambridge & The Medical Research Council Cancer Cell Unit

演題：Chromosomal instability in cancer pathogenesis and treatment

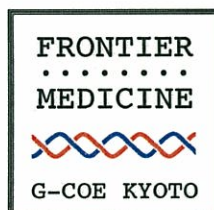
要旨：

Instability of chromosome structure or number is a hallmark of common epithelial malignancies. In this talk, I will describe recent studies on cancer-associated alterations in the pathways that preserve chromosome stability, and their role in cancer pathogenesis and treatment.

Germline mutations in the breast cancer susceptibility gene, BRCA2 give rise to numerical and structural chromosomal aberrations (reviewed in 1). One major role of BRCA2 is in the control of the RAD51 recombinase during the reactions that lead to DNA repair by homologous DNA recombination. Varshavsky's N-end rule has been used to create a thermo-sensitive form of RAD51 in vertebrate cells, revealing the co-ordination between DNA replication and homologous recombination during cell cycle progression (2). The BRC repeat motifs in BRCA2, conserved in sequence and spacing between its mammalian orthologues, play a critical role in RAD51 regulation. We have combined biochemical approaches with methods for single-molecule detection to demonstrate that the BRC repeats have opposing effects on the binding of RAD51 to single- versus double-stranded DNA molecules; these effects reinforce one another to promote homologous DNA recombination (3, 4, 5). It has been proposed that a carboxyl-terminal RAD51-binding region in BRCA2, distinct from the BRC repeats, is also critical for homologous DNA recombination. We have used biochemistry and somatic cell genetics to show that the binding of RAD51 to this C-terminal BRCA2 motif is dispensable for the execution of homologous recombination in cells, but instead, has a new function in co-ordinating the termination of DNA repair with entry into mitosis (6). The implications of our findings for the pathogenesis and treatment of human cancers associated with BRCA2 mutations will be discussed.

Pathways that control chromosome segregation affect not only the pathogenesis of cancer, but also the sensitivity of cancer cells to anti-mitotic drugs. We have carried out a functional genomics screen for genes whose activity influences mitotic arrest induced by taxanes, and find a new enzymatic component of the APC/C whose activity is essential for this response, but not for normal mitosis (7).

1. Venkitaraman AR. (2009) *Annu Rev Pathol* 4, 461.
2. Su, X., J.A. Bernal & A.R. Venkitaraman (2008). *Nature Struct Mol Biol* 15, 1049.
3. Carreira A, Hilario J, Amitani I, Baskin RJ, Shivji MK, Venkitaraman AR, Kowalczykowski SC. (2009) *Cell* 136, 1032.
4. Shivji MK, Mukund S, Rajendra E, S Chen, Short JM, Klenerman D, Venkitaraman AR. (2009) *Proc Natl Acad Sci USA* (In press)
5. Rajendra E, Venkitaraman AR. (2009) *Nucleic Acids Res* (In press)
6. Ayoub NA, Rajendra E, Jeyasekharan AD, Su X, Mahen RJ, Venkitaraman AR. (2009) *Curr Biol* (In press)
7. Garnett MJ, Mansfeld J, et al (2009) *Nature Cell Biology* (In press)



主催 グローバルCOE

連絡先：放射線遺伝学 (Radiation Genetics)  
武田 俊一 (Shunichi Takeda) 内線 (ext.4410)