CRBM external seminar

September 14th, 2023 11:00 am Amphi Délégation CNRS - DR13 - 1919 Route de Mende

DNA strand break repair and links to human disease

Steve WEST, PhD, FRS, FMedSci

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Professor Stephen Craig West FRS is a British biochemist and molecular biologist known for pioneering studies on genome instability diseases including cancer, and discovered many of the cellular enzymes responsible for DNA repair. Steve obtained his PhD in 1977 from Newcastle University. He continued his training at Yale University as a post-doc before moving back to the UK to become a group leader at Clare Hall laboratories (Imperial Cancer Research Fund). He is now Senior Group Leader at the Francis Crick Institute in London (Cancer Research UK). He is an honorary Professor at University College London, and at Imperial College London. He has been awarded many prizes for his research, including the Louis-Jeantet Prize for Medicine in 2007, the Genetics Medal in 2012, and the Lifetime Achievement Award in Cancer Research in 2018. In 2022 he was awarded the Royal Medal. He is a Fellow of the Royal Society, the Academy of Medical Sciences, an International Member of the National Academy of Sciences, and an International Honorary Member of the American Academy of Arts and Sciences.

Abstract

DNA instability is a major cause of inheritable human diseases, such as cancers or neurological disorders, and is also responsible for many aspects of the ageing process. Fortunately, our cells possess a large repertoire of DNA repair processes that maintain our DNA in perfect condition.

Steve West's laboratory has pioneered the study of enzymes that promote the intricate DNA interactions necessary for the recombinational repair of DNA strand breaks. Using biochemistry, structural biology and molecular genetics, his lab has determined mechanisms of DNA repair that act to prevent tumourigenesis, in particular focusing on the BRCA2 protein that is defective in inheritable breast and ovarian cancers.

In this lecture, Steve will present new cryo-EM studies that define the structure and mechanism of action of the human RAD52 and RAD51 paralog complexes, and will provide new insights into novel therapeutic approaches that aim to kill *BRCA*-defective cancers.

Selected publications

Greenhough, L.A., Liang, C.-C., Belan, O., Kunzelmann, S., Maslen, S., Rodrigo-Brenni, M.C., Anand, R., Skehel, M., Boulton, S.J., and West, S.C. (2023). Structure and function of the RAD51B-RAD51C-RAD51D-XRCC2 tumour suppressor. Nature *619*, 650-657.

Benitez, A., Sebald, M., Kanagaraj, R., Rodrigo-Brenni, M.C., Chan, Y.W., Liang, C.-C., and West, S.C. (2023). GEN1 promotes fragile site expression. Cell Rep. *42*, 112062.

Kanagaraj, R., Mitter, R., Kantidakis, T., Edwards, M.M., Benitez, A., Chakravarty, P., Fu, B., Becherel, O.J., Yang, F., Lavin, M.F., *et al.* (2022). Integrated genome and transcriptome analyses reveal the mechanism of genome instability in Ataxia with Oculomotor Apraxia 2. Proc. Natl. Acad. Sci .U. S. A. *119*, e2114314119.

Fugger, K., Bajrami, I., Silva Dos Santos, M., Young, S.J., Kunzelmann, S., Kelly, G., Hewitt, G., Patel, H., Goldstone, R., Carell, T., *et al.* (2021). Targeting the nucleotide salvage factor DNPH1 sensitizes BRCA-deficient cells to PARP inhibitors. Science *372*, 156-165.