D-MEM PhD-UNIMI | Doctorate program Milan EXPERIMENTAL MEDICINE

BIOMETRA

UNIVERSITÀ DEGLI STUDI DI MILANO

International PhD Program in Experimental Medicine

D-MEM SEMINAR

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IFOM ETS The AIRC Institute of Molecular Oncology
Dept of Oncology and Hematology-Oncology, University of Milan

May 9, 2023- 4.00 pm
Aula D, LITA Segrate

CAUSES AND CONSEQUENCES OF DNA REPLICATION STRESS IN CANCER AND STEM CELLS

Replication forks are constantly challenged by endogenous and exogenous threats that induce replication stress potentially impacting on the accuracy and the efficiency of DNA duplication, especially in large and complex genomes. Several DNA repair pathways monitor and counteract the occurrence of such stress. Somatic to cancer cell transformation often occurs when these repair pathways fail. Among these there are DNA repair events coordinated by homologous recombination (HR) and checkpoint proteins. Using biochemical tools to study essential DNA replication and repair proteins, combined with DNA electron-microscopy, we discovered the role of HR proteins, including RAD51 and BRCA1/2, in preventing nascent DNA degradation and single-stranded DNA gaps accumulation. Mutations in HR genes predispose to tumor formation as they favour low fidelity DNA repair pathways that fuel genome instability, allowing uncontrolled growth and proliferation of cancer cells. As deletion of HR genes is mostly lethal in normal cells their loss is often compensated by alterations that allow HR-defective cancer cells to survive. Among these there is the overexpression of Polymerase Theta (POLθ), which promotes the repair of DNA double-strand breaks (DSBs) resulting from collapsed forks in HR-defective tumors. Inactivation of POLθ results in synthetic lethality with the loss of HR genes BRCA1/2. However, it was unclear whether POLθ-dependent DNA replication prevents HR deficiency associated lethality. We have recently shown that POLθ suppresses ssDNA gaps accumulating at replication forks in the absence of BRCA1, BRCA2 or RAD51. Inhibition of POLθ DNA polymerase activity leaves fork gaps unprotected, enabling their cleavage by the MRE11 endonuclease, which produces forks with single-ended DSBs. Fork breakage results in MRE11-NBS1-CtIP dependent lethality of HR-defective cells. These results suggest that, in addition to their well-established role in DSB repair, POLθ promotes genome stability by protecting replication forks from nuclease-mediated rupture. Several questions remain unresolved in the DNA replication stress field. Among these how persistent DNA replication stress initiates tumor formation and how long-term genome stability is maintained in stem cells. During the seminar I will discuss published and ongoing work on these topics.

The streamed seminar will be available:
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