QST · NIRS - RBC International Symposium
Rethinking Radiation Injury - Impact of Cytoplasmic DNA -

9:30, November 15, 2019
Part 1: Basic Biology

Confirmed Speakers
Roger Greenberg
University of Pennsylvania, U.S.A.
Tokuko Haraguchi
Advanced ICT Research Institute, NICT, Japan
Baoxue Ge
Tongji University, China

13:00, November 16, 2019
Part 2: Cancer Therapy

Confirmed Speakers
Sandra Demaria
Weill Cornell Medical College, U.S.A.
Akinori Takaoka
Hokkaido University, Japan
Yea-Lih Lin
Institute of Human Genetics, France

This symposium is a part of the 62nd annual meeting of the Japanese Radiation Research Society, JRRS.

Venue: Symposium Hall, International Science Innovation Building, Kyoto University
(http://62jrrs.rbc.kyoto-u.ac.jp/venue.html)

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- Impact of Cytoplasmic DNA -

Part 1: Basic Biology (9:30, November 15, 2019)
Ionizing radiation causes mitotic chromosome segregation errors and is involved in the formation of micronuclei. The destruction of the micronuclei and the resulting appearance of cytoplasmic DNA can cause radiation damage at the cellular level.

**Dr. Greenberg**’s group has previously reported that progression through mitosis is a critical step for enabling damaged genomic DNA to enter the cytoplasm and elicit inflammatory cytokine signals that activate immune responses to tumors. His talk at this symposium will focus on mechanisms that enable damaged genomic DNA to be recognized and responded to by pattern recognition receptors in the cytoplasm. Focus will be placed in the cell cycle and DNA repair mechanisms that either suppress or promote the presence of cytoplasmic DNA. How the responses to cytoplasmic DNA affect immune mediated destruction of tumors will also be addressed.

**Dr. Haraguchi**’s group has found that the micronuclei were gradually lost from the cell over time. By using live CLEM (correlative light-electron microscopy), they have followed the process of how the micronucleus was lost from the cell. Results showed that reformation of the nuclear envelope was often incomplete in the micronuclei after mitosis. Those micronuclei lacking the complete nuclear envelope were surrounded by the autophagosome or endosome/lysosome. She will present the results indicating that the micronucleus possessing incomplete nuclear envelope can be discarded outside of the cells.

**Dr. Ge**’s group has previously reported that nuclear cGAS suppresses homologous-recombination-mediated repair and promotes tumour growth, and that cGAS therefore represents a potential target for cancer prevention and therapy. He will present their new findings in the symposium.

Part 2: Cancer Therapy (13:00, November 16, 2019)
Genomic instability and radiotherapy-induced DNA damage are associated with accumulation
of DNA into the cytosol, where it activates canonical pathways activated by viral infections and involved in induction of adaptive immune responses.

Dr. Demaria’s group has demonstrated that the cancer cell-intrinsic interferon type I (IFN-I) response induced by cytosolic DNA via the cGAS/STING pathway is critical for the ability of radiotherapy to induce systemically effective anti-tumor immunity in combination with immune checkpoint blockade therapy. Cytosolic DNA accumulation is dependent on the radiation dose and is regulated by the exonuclease TREX1. Further, exosomes secreted by the irradiated cancer cells shuttle IFN-stimulatory DNA to dendritic cells and stimulate STING-dependent IFN-I production by the recipient DCs. She will present results of current study exploring the nature of the DNA that efficiently stimulates this acute IFN-I production, which is key for radiotherapy-induced viral mimicry.

During viral infection, virus-derived nucleic acids are mainly targeted by certain pattern recognition receptors. In most cases, such viral sensors activate TBK1-dependent IFN pathway for inducing antiviral activities. On the other hand, it has been shown that these nucleic acid sensors also detect host-derived nucleic acids during DNA damage induced by radiation and chemotherapy, etc., which activates their downstream signalings to induce type I/III interferons and other cytokines, which cause inflammatory responses. Dr. Takaoka will talk about the recent data from his group regarding a novel regulatory mechanism for activation of cytoplasmic nucleic acid sensor-mediated signalings during DNA damage.

Replication stress is commonly referred as the transient stalling or collapse of replication forks in response to endogenous or exogenous obstacles during DNA replication. Dr. Pasero’s group has recently provided the first molecular evidence linking replication stress and type I interferon response. In this symposium, Dr. Lin from Dr. Pasero’s lab will discuss the extension of their finding in deciphering the etiology of replication stress-induced pathologies.