九州大学ストックホルム・リエゾンオフィス（欧州拠点）

欧州研究者アカデミックセミナー　第１回

KYUSHU UNIVERSITY STOCKHOLM ESTABLISHED

Academic Seminar :

Molecular mechanism on the nuclear and mitochondrial DNA maintenance

REGISTER NOW

Date & Time

November 25

Monday 2024

13:00 - 14:30

Venue

Lecture Hall 2, 3rd floor
Faculty of Pharmaceutical Sciences Bldg.
薬学部本館３階　第２講堂

Language　English (no interpretation)

Nuclear and mitochondrial genomes must be inherited properly, and the failure of genomic DNA maintenance often leads to genome instability and various diseases including cancer.

In this seminar, two guest speakers from Europe will talk about the latest findings on the molecular mechanism of the replication restart by PrimPol DNA primase/polymerase and the mtDNA metabolism.

Guest Speakers:

Sjoerd Wanrooij
Associate Professor
Medical Biochemistry and Biophysics
Umeå University
Sweden

María Isabel Martínez-Jiménez
Research Fellow
Centro de Biología Molecular Severo Ochoa (CBMSO)'
Spain

Organizer : Kazutoshi Kasho
Assistant Professor, Pharmaceutical Sciences Kyushu University

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Mitochondrial DNA (mtDNA) metabolism alterations promote inflammatory gene expression in senescent cells.

◯Sjoerd Wanrooij1, Valentin L'Hote1, Lisa Marchhart1, Alma Vennberg1, Maxime Donzel1, Erik Chorell1
(1. Umea university, Sweden)

Chemotherapy induces the formation of senescent cells, which secrete a complex collection of factors termed the SASP (senescence-associated secretory phenotype), contributing to a pro-tumorigenic environment. It is established that counteracting senescent cells in cancer potentiates chemotherapy, limits its side effects, and prevents tumor relapse.
Understanding how the SASP expression program is regulated is fundamental in order to harness the potential of targeting senescent cells to improve anticancer treatment. In the recent years, it has been shown that mitochondrial DNA (mtDNA) leaks to the cytosol of senescent cells and activates innate immunity sensors, thereby promoting SASP expression. Mechanisms for the mtDNA cytosolic release itself in senescence, via partial mitochondrial permeabilization, have been characterized. However, how mtDNA replication and maintenance are altered in senescent cells and support mtDNA cytosolic release and pro-tumorigenic SASP expression, remains unexplored. We are characterizing senescence-associated alterations in mtDNA metabolism and how these contribute to the SASP. We found that the mitochondrial replisome undergoes recomposition during senescence progression, leading to increased replication and promotion of mtDNA cytosolic release. Based on these results, we are developing pharmacological strategies targeting mtDNA metabolism in senescent cells to inhibit SASP expression. Our perspective is to hopefully propose new adjuvant therapies to potentiate chemotherapy and limit its side effects.

The pillars of the human DNA primase/Polymerase, PrimPol

María I. Martínez-Jiménez, Marcos Jiménez-Juliana, Cristina Velázquez-Ruiz, Susana Guerra-González and Luis Blanco

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PrimPol is a DNA primase/polymerase from the Archaeo-Eukaryotic Primase (AEP) superfamily that enables replication restart by synthesizing DNA primers ahead of stalled replication forks at both nucleus and mitochondria. Human PrimPol catalysis relies on a single active site that harbors the catalytic carboxylates acting as metal ligands, and highly conserved residues, which favor and stabilize 3´-dNTPs.
The exclusive feature of primases is dimer synthesis, that requires the ordered binding of two nucleotides: first, the one that occupies the elongation or 3´ site and then, the one at the initiation or 5´ site. Further nucleotide additions to the dimer allow the synthesis of the mature primer.

HsPrimPol requires a specific Zn-finger domain (ZnFD) to stabilize the binding of a NTP at the 5´site. We found that the ZnFD contains an electropositive pocket, whose charged residues are essential for the bonding of the 5´-NTP triphosphate during dimer synthesis. In addition, this interaction is maintained during the elongation process to ensure the synthesis of a mature primer, and therefore the ZnFD behaves as a processivity factor. This is especially relevant for growing primers across DNA lesions. The importance of specific dNTP ligands at the 3´site for the different synthetic reactions catalyzed by HsPrimPol (dimer synthesis, elongation, lesion bypass...) has been studied.

We have modelled how HsPrimPol´s pillars move from dimer synthesis to primer maturation, implying conformational changes that progressively separate the ZnFD from the catalytic core, but maintaining the strong interactions with the 5´triphosphate during translocation of the growing primer.