第１０４回 病態生化学セミナー

日時：平成２８年１１月１７日（木曜日）午後６時００分～

場所：医学部講義棟１階 国際交流ラウンジ

演題：新規DNA修復遺伝子WDR4の異常により発症する発育異常症の分子病態解析

A germline mutation in the WDR4 gene causes severe developmental abnormalities associated with genome instability

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DNA damage response and DNA repair processes are critical for the maintenance of genome integrity. Various human pathological conditions including neurodegeneration, immunodeficiency, developmental defects, microcephaly as well as predisposition to cancer are often associated with defects in the DNA repair system.

We focused on microcephaly and primordial dwarfism cases to identify new DNA repair gene mutations and to understand the pathogenesis underlying the neurodegeneration by genome instability during development. From a screening and diagnoses of ~200 microcephaly cases, we recently identified a missense pathogenic mutation in the WDR4 gene in patients with severe growth deficiency, microcephaly, thrombocytopenia and nephrotic syndrome.

The budding yeast orthologue of WDR4 gene product, Trm82, is characterised as a component of a tRNA methyltransferase complex that consists of Trm8 (also known as METTL1 in human) and is required for the N7-methylguanosine (m7G) modification and maturation of pre-phenylalanyl (Phe)-tRNA molecules. Though, the functions of humanWDR4 gene and its mammalian homologues are not well determined.

Here we show that WDR4 is recruited to the sites of DNA damage, and cells from a patient are sensitive to various genotoxic stresses. A mutant form identified in the WDR4 patients is not able to alleviate cell survival after DNA damage, in spite of restoration of the expression levels of METTL1. We find some DNA damage responsive proteins as potential WDR4 interactors using SILAC-based quantitative mass spectrometry. Our results provide a molecular explanation of how WDR4 dysfunction causes severe developmental abnormalities associated with genome instability.

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博士課程選択必修科目: 基礎医科学(D3)、

博士課程選択科目: 細胞生物学I(D6)、老化II(D20)、発生生物学I (D15)、発癌I (D22)、腫瘍生物学I (D24)、II (D25)、III (D26)、臨床腫瘍学I (D28)、II (D29)、III (D30)、

IV (D31)、V (D32)、VI (D33)、地域がん治療学 (D37-1) 、口腔腫瘍学 (D37-2)、薬物動態学I (D70)、腫瘍免疫学I (D79)、理工医学のための生物材料学(D103)

医科学専攻(修士課程)選択科目:
腫瘍の発生・増殖とその制御 (M23)、理工医学のための生物材料学の基礎 (M34)
を履修している学生は、できる限りこのセミナーに出席してください。