THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

醫療科技及資訊學系
Department of Health Technology and Informatics

Nucleoporins Mitotic Functions and Oncogenesis

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Venue: N113, 1/F, The Hong Kong Polytechnic University

Abstract:

Intracellular trafficking between the nucleus and the cytoplasm is accomplished through the nuclear pore complex (NPC), which are thousands of cylindrical holes, at sites where inner and outer nuclear membranes join. Several NPC that mediate transport of RNA or macromolecules into and out of the nucleus have been implicated in mitosis. The NPCs are made of ~30 different proteins named nucleoporins (Nups). Nucleoporins are designated "Nup" followed by their predicted molecular weight; they are modular in their frequent use of the same structural motifs (coiled-coils, α solenoids and β propellers). Approximately a third of nucleoporins contain domains of phenylalanine-glycine (FG) motifs interspersed with spacer sequences. These repeat domains are natively unstructured and serve as interaction sites for transport receptors (karyopherins), which escort cargo through the pores. During mitosis, these nucleoporins are involved in molecular networks that function in a variety of mitotic processes, including chromosome condensation, sister chromatid cohesion, kinetochore assembly and spindle formation.

Many human cancers have irregular chromosome content, a condition known as aneuploidy. Chromosomal translocations involving chimeric fusions of the nucleoporin NUP98 protein have often been described in acute myelogenous leukemia (AML). All the fusion proteins have an identical NUP98 N terminus, which contains the GLEBS motif for interaction with the mRNA export factor RAE1 and FG repeats that associate with the transcription factors HDAC1 and p300. It is virtually unknown whether these interaction partners affect leukemogenesis. We previously showed that RAE1 depletion caused aneuploidy, which enhanced tumorigenesis during mitosis. We speculated that RAE1 may also be directly involved in NUP98 fusion-mediated leukemogenesis. Recently, we found that RNA interference (RNAi)-mediated knockdown of NUP98 caused severe chromosome segregation defects and disrupted RAE1 but not HDAC1 expression and localization. We performed rescue experiments to confirm that the RAE1-NUP98 complex orchestrates proper chromosome segregation. Interestingly, we found diverse behaviours of NUP98 and the leukemogenic fusion protein NUP98-HOXA9 throughout the cell cycle. Strikingly, in NUP98-HOXA9-transfected cells, RAE1 protein were reduced and mis-localized. Our cellular interpretations were further confirmed by NUP98-HOXA9 transgenic mice and the NUP98-HOXA9 AML patient. These data suggest that RAE1 orchestrates NUP98-mediated leukemogenesis and raise the possibility that targeting this negative feedback loop may provide a new strategy for the therapy of aggressive leukemias. In this talk, I will discuss this sprouting area and the possible mitotic functions of other nucleoporins during cell division.

Reference:

1. Funasaka T et.al. (2011) Cell Cycle 10(9):1456-1467. [IF 5.359]
2. Funasaka T and Wong RW (2011) Cancer Metasta Rev. 30(2):239-251. [IF 10.573]
3. Nakano H et.al. (2011) Cell Cycle 10(3):425-433. [IF 5.359]
4. Nakano H et.al. (2010) J. Biol. Chem. 285(14): 10841-10849. [IF4.773]
5. Wong (2010) Cell Cycle 9(9):1754-1758. [IF 5.359]
6. Wong (2010) Cell Cycle 9(1): 198-200. [IF 5.359]

About the Speaker:

Please visit the website - http://fsowonglab.w3.kanazawa-u.ac.jp/sample1.html

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All are Welcome!