【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Biological Sciences)

Title of Project : Investigation of the novel mechanisms underlying tumorigenesis due to aberrant Wnt signal networks

Akira Kikuchi
(Osaka University, Graduate School of Medicine, Professor)

Research Project Number : 16H06374 Researcher Number : 10204827
Research Area : Biological Sciences
Keyword : Wnt signaling, Arl4c, Dkk1, CKAP4, Wnt5a

【Purpose and Background of the Research】

Wnts are secretory proteins that are conserved evolutionally and regulate two intracellular signaling pathways: β-catenin-dependent and -independent. Both pathways are essential for animal development, whereas the roles of Wnt signaling in the post-natal life are not well understood.

Wnt signaling abnormalities are frequently observed in human cancers, and the extensive trials to develop new cancer therapeutics which target Wnt signaling molecules, especially the β-catenin-dependent pathway components, have been long continued. The good outcomes, however, have not been obtained yet. Evidence has accumulated that the β-catenin-independent pathway is also involved in tumorigenesis, but the significance is not fully understood because the activation of Wnt5a/β-catenin-independent signaling promotes or suppresses tumorigenesis in a cancer cell context.

In this study we aim to clarify unresolved issues in the Wnt signaling field. Especially the mechanisms by which novel downstream signaling of the β-catenin pathway causes tumor formation and those by which the β-catenin-independent pathway controls tumorigenesis and inflammation will be clarified (Figure 1).

【Research Methods】

1. Regulation of expression and mode of action of Arl4c in tumorigenesis

We identified Arl4c as a new downstream molecule of the β-catenin -dependent pathway. How Arl4c is expressed and activated and how the expression causes tumorigenesis are examined.

2. Modes of activation and action of Dkk1-CKAP4 signaling in tumorigenesis

CKAP4 was identified as a novel receptor of Dkk1, a direct target of the β-catenin-dependent pathway. How Dkk1-CKAP4 signaling promotes tumorigenesis is investigated.

3. Regulation of expression and mode of action of Wnt5a in tumorigenesis with inflammation

How Wnt5a is expressed in fibroblasts and cancer cells by inflammatory cues and how cancer cells and immune cells are mutually interacted are examined.

【Expected Research Achievements and Scientific Significance】

The following mechanisms would be clarified.

1. The molecular mechanism by which the novel signaling downstream of the β-catenin-dependent pathway causes tumor formation.
2. The molecular mechanism by which the Wnt5a/ β-catenin-independent pathway causes tumor formation and inflammation.

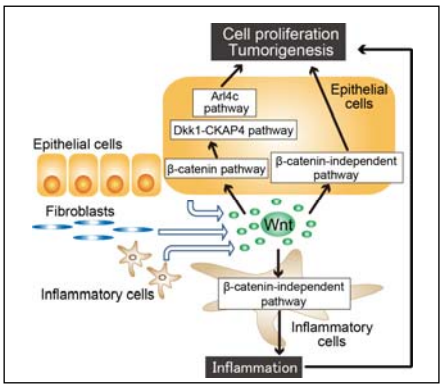

Figure 1

【Publications Relevant to the Project】

・Kimura, H., Fumoto, K., Shojima, K., Nojima, S., Osugi, Y., Tomihara, H., Eguchi, H., Shintani, Y., Endo, E., Inoue, M., Doki, Y., Okumura, M., Morii, E., and Kikuchi, A. CKAP4 is a Dickkopf1 receptor and is involved in tumor progression. J. Clin. Invest. doi:10.1172/JCI84658, 2016

・Matsumoto, S., Fujii, S., Sato, A., Ibuka, S., Kagawa, Y., Ishii, M., and Kikuchi, A. A combination of Wnt and growth factor signaling induces Arl4c expression to form epithelial tubular structures. EMBO J. 33, 702-718, 2014

【Term of Project】

FY2016-2020

【Budget Allocation】

136,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.osaka-u.ac.jp/pub/molbiobc/
akikuchi@molbiobc.med.osaka-u.ac.jp