Molecular Mechanism of Anchorage-Dependent and -Independent S Phase Onset

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【Outline of survey】

Besides hematopoietic cells, virtually all the cells constituting the entire body of adult mammals require anchorage to the extracellular matrix or its equivalent for their proliferation and survival, and without anchorage to such substance, they arrest in the G_1 phase of the cell cycle and eventually die of an apoptosis named anoikis. Upon malignant transformation, they acquire the ability to perform proliferation without anchorage, which is the foundation for tumorigenicity and metastatic capability of malignant cells. Recently we discovered that anchorage deprivation-induced G_1 arrest is resulted from the inactivation of G_1 phase cyclin-dependent kinases and the termination of Cdc6 expression, the latter of which via Rb-independent transcriptional repression and lysosomal cathepsin-led proteolytic degradation, and furthermore we found the critical involvement of the p53 tumor suppressor protein in anchorage deprivation-invoked lysosomal permeabilization.

In this research, we will address the molecular mechanism and signal cascade dictating anchorage signal-controlled lysosomal permeabilization and Rb-independent transcriptional repression of the cdc6 gene.

【Expected results】

The fundamental mechanism of malignant transformation will be understood with the possible finding of new effective cancer therapy targets. One of the major unsolved questions in cancer research: how p53 exerts its tumor suppressor function will be solved. The finding of a role for lysosomal cathepsins in cell cycle control would open a new research field concerning the lysosome as fine cellular control machinery, not simply an endocytosed protein degradation apparatus.

【References by the principal researcher】

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• Chen, Q., Lin, J., Jinno, S. and Okayama, H.; Overexpression of Cdk6-cyclin D3 highly sensitizes cells to physical and chemical transformation. 2003, Oncogene **22**, 992-1001.

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【Homepage address】 http://www.cellcycle.m.u-tokyo.ac.jp