公益財団法人 セコム科学技術振興財団
研究成果報告書

研究課題名
異常細胞排除機構を利用した先制医療法の開発

Development of pre-emptive medical methods using the mechanism of abnormal cell elimination

研究期間
令和 2 年 10 月　～　令和 6 年 9 月

報告年月
令和 6 年 12 月

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Abstract

When tissues and organs are subjected to various types of stress, abnormal cells such as damaged cells, genetically mutated cells and senescent cells arise within the normal cell population. Young, healthy tissues/organs have the ability to eliminate these abnormal cells (abnormal cell elimination capacity) and to fill the space vacated by the proliferation of surrounding normal cells (compensatory cell proliferation capacity). Eliminating abnormal cells and maintaining an appropriate number of cells is essential for the long-term normal functioning of tissues and organs. Using adult mouse liver and mammalian cultured cells, the applicants have discovered and reported that the "phosphorylation signal Hippo-transcription-coupled factor YAP pathway induces the elimination of abnormal cells" (*Nature* 2015; *Sci Rep* 2016; *Nat Commun* 2017; *Cancers* 2018;. *Biochem Biophys Res Commun* 2021; *Cancer Science* 2022). If abnormal cells can be eliminated in the early stages of their emergence, it is expected to reduce the risk of disease and extend healthy life expectancy without loss of physiological function of tissues and organs. In view of the aging population in Japan, "elucidation of the mechanism of abnormal cell elimination and development of pre-emptive medical methods utilising this mechanism" is an important issue to achieve an increase in healthy life expectancy. However, there are still many unresolved aspects of these molecular mechanisms. In this study, we aimed to elucidate the molecular mechanisms of "cell exclusion signals" that induce abnormal cell exclusion and the molecular mechanisms required for "compensatory cell proliferation" to fill the vacant space.

Results, 1) actin fibres, which control cell morphology and motility, are involved during cell exclusion, and we found that the expression of Rho GEF and Rho GAP genes, which control actin fibre elongation and shortening, is induced, 2) the expression of chemokine genes, which induce macrophages to phagocytise abnormal cells, is also induced. It was also suggested that 3) open chromatin consisting of DNA and proteins in the nucleus is induced, and that transcription factors CTCF, which regulates chromatin structure, and TEAD, which binds to YAP, bind to it (paper in preparation). However, the actual nature of the 'cell exclusion signal' from the plasma membrane to the nucleus remains unclear, and 4) Interesting findings on hepatocyte proliferation. The applicant has already generated Mkk7 flox/flox Synapsin I-Cre (Mkk7 cKO) mice lacking the mature neuron-specific stress kinase MKK7, and found that these mice show age-dependent (6 month-old vs. 10 month-old) abnormal axonal transport capacity, muscle atrophy and reduced motor capacity (sarcopenia-like phenotype) is induced. When the mice were subjected to liver injury, we found that the amount of neurotransmitters secreted from the autonomic nervous system decreased in 10 month-old mice compared to 6 month-old mice, and that the hepatocyte proliferative capacity decreased, resulting in lethality. The findings suggest an essential role of the autonomic nervous system in the liver in hepatocyte proliferation and liver regeneration (paper in preparation).