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

Broad Section H

Title of Project： **Deciphering Molecular Basis for the Anti-Oxidative Stress Response and Application of the Basis for Disease Prevention and Therapy**

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Research Project Number：19H05649　Researcher Number：50166823
Keyword：Stress response, KEAP1-NRF2 system

【Purpose and Background of the Research】

Environmental factors such as dietary poison, ultraviolet, and air pollution often cause redox disturbance and leads to irreversible changes of biomolecules that might explain many types of disorder. The KEAP1-NRF2 system is one of the most important defense mechanisms against the redox disturbance. In addition to the anti-oxidant function of NRF2, we recently clarified that NRF2 has a potent anti-inflammatory function, which is likely to result from direct inhibition of pro-inflammatory cytokine production by NRF2. Considering recent studies describing the increased oxidative stress and smoldering chronic inflammation in the pathological basis of many disorders, including Alzheimer's disease, arthritis and type 2 diabetes, we can expect that NRF2 activation is effective for prevention and treatment of the chronic diseases and achievement of healthy aging. The goal of this research is to clarify new mechanisms of the KEAP1-NRF2 system and to explore the effectiveness of NRF2 activation for anti-disease strategy toward health and longevity. In this research proposal, we will clarify basic molecular mechanisms how the KEAP1-NRF2 system is regulated, contributions of NRF2 to the prevention of stress-related disorders, and relation among the functionality of the

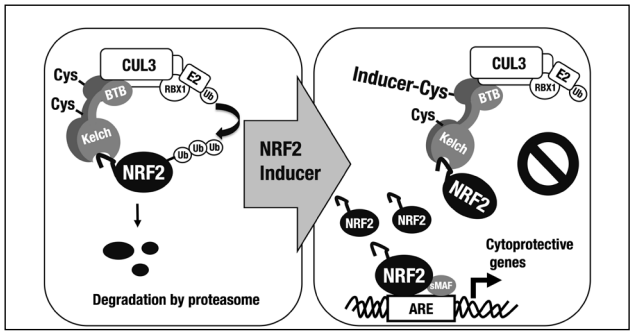

Figure 1 KEAP1-NRF2

KEAP1-NRF2 system and organismal redox balance and health.

【Research Methods】

We will clarify basic molecular mechanisms how the KEAP1-NRF2 system is regulated, contributions of NRF2 to the prevention of various disorders, and relation among the functionality of the KEAP1-NRF2 system and organismal redox balance and health.

1) ROS sensor(s) of KEAP1. To clarify the function of the oxidative stress sensor *in vivo*, we are planning to generate KEAP1 mutant knock-in lines of mice that will be unable to response to hydrogen peroxide.

2) Structure analysis of NRF2-KEAP1-CUL3 complex. To understand this mechanism how KEAP1's structure changes in response to stress to regulate NRF2's activity, structural analysis of full-length KEAP1 must be undertaken. We will endeavor to reveal the structure and function of KEAP1 in complex with NRF2 and CUL3 by combining X-ray crystallography, cryo-EM and NMR spectroscopy analyses.

3) Physiological analysis of NRF2 in prevention of aging related disease. We have developed several lines of mice for targeting KEAP1 or NRF2, and also obtained disease model animal for Alzheimer's disease, arthritis and type 2 diabetes. To clarify contribution of NRF2, we are generating compound mice having loss- or gain-of-NRF2 function in these disease model mice.

【Expected Research Achievements and Scientific Significance】

As an outcome of this research, we will consolidate an idea that NRF2 activation is a general target for an anti-disease strategy. Extension of health span is an urgent need in the current super-aging society. To this end, long-term and preventive intervention with low costs is required. A good thing about the KEAP1-NRF2 system is that NRF2 can be appropriately activated by naturally occurring phytochemicals contained in vegetables and other food. From these social perspectives, we believe that NRF2 is a perfect target for anti-aging strategy with sufficient practicality.

【Publications Relevant to the Project】

- **Yamamoto M**, Kensler TW, and Motohashi H. The Keap1-Nrf2 System: a thiol-based sensor-effector apparatus for the maintenance of redox homeostasis. ***Physiol Rev*** 98, 1169-1203. (2018)
- Suzuki T, **Yamamoto M**. et al, Molecular mechanism of cellular oxidative stress sensing by Keap1. ***Cell Reports*** *in press* (2019)

【Term of Project】 FY2019-2023

【Budget Allocation】 153,000 Thousand Yen

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