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

Integrated Disciplines (Complex Systems)

Title of Project : Search for novel modulators of cereblon, the target of thalidomide that regulates neural stem cell proliferation and differentiation

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Research Project Number : 17H06112 Researcher Number : 80107432
Research Area : Integrated Disciplines(Complex Systems)
Keyword : Brain･Neuron, Development, Regenerative medicine, Biomolecules, Pharmacy

【Purpose and Background of the Research】

Using our original affinity nanobead technology, we identified cereblon (CRBN) as a target of thalidomide teratogenicity, and demonstrated that CRBN is a substrate receptor of E3 ubiquitin ligases (Science, 2010). Furthermore, through collaborative research with Celgene Corp. in the US, we clarified the involvement of CRBN in the anti-cancer effects and immunomodulatory effects of immunomodulatory drugs (IMiDs), including thalidomide. In addition, we identified the novel thalidomide derivative CC-885, which exerts therapeutic effects without immunomodulatory effects against acute myelocytic leukemia, and clarified its mechanisms of action (Nature, 2016). We therefore named thalidomide and its derivatives that exert therapeutic effects via CRBN as “CRBN modulators”, and we showed that each modulator recruits, ubiquitinates and degrades specific ates (Nature, 2015).

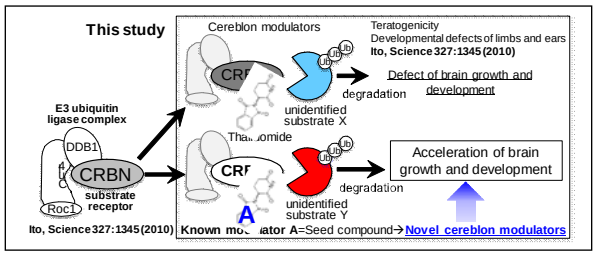

Fig. Conversion of substrate specificity by CRBN modulators

To understand the role of CRBN in brain growth and development, we demonstrated that treating zebrafish embryos with thalidomide inhibits brain development, and results in brain atrophy and a decrease in neural stem cell number via CRBN. Inhibition of CRBN expression also resulted in brain atrophy similarly to thalidomide, and CRBN overexpression resulted in brain enlargement and an increase in neural stem cell number. The aim of our research is to understand the role of CRBN in brain growth and development, to search for and identify novel CRBN modulators and substrate proteins, and to understand the mechanisms of action of CRBN modulators.

【Research Methods】

①We will identify downstream factors of CRBN and thalidomide using transcriptome and proteome analyses. ②We will establish zebrafish expressing human CRBN, and we will ③identify novel CRBN modulators that activate neural stem cell growth via chemical library screening. ④ Using our affinity nanobead technology, we will isolate and identify specific substrates of the novel CRBN modulators. ⑤We will characterize the substrates and their associated proteins, and ⑥ using cultured human neural stem cells and higher-order experimental animals, we will analyze the function of the identified substrates. ⑦We will clarify the mechanisms of action of novel CRBN modulators in neural stem cells during early development and in the mature brain, and ⑧using patient-derived cultured neural stem cells, we will explore the application of these modulators in the treatment of human brain disorders and regenerative medicine.

【Expected Research Achievements and Scientific Significance】

An epoch-making technology that enables brain regenerative medicine using endogenous neural stem cells has not been established to date. If novel CRBN modulators that can specifically control brain stem cells are established through our research, their application in the treatment of brain disorders, such as autism, depression, and dementia, as well as regenerative medicine are anticipated. Furthermore, our research is also expected to significantly contribute to basic neuroscience research, via clarification of the control network centered around CRBN, and the development of various CRBN modulators are also anticipated.

【Publications Relevant to the Project】

･Ito, T., Ando, H., Yamaguchi, Y., Handa, H., et al., Identification of a primary target of thalidomide teratogenicity. Science, 357, 1345-1350, 2010.
･Ito, T and Handa, H. Another action of a thalidomide derivative. Nature, 523, 167-168, 2015.

【Term of Project】 FY2017-2019

【Budget Allocation】 139,300 thousand yen

【Homepage Address and Other Contact Information】

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