

論文 / 著書情報
Article / Book Information

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Title(English)	MKRN2 is a novel ubiquitin E3 ligase for the p65 subunit of NF- κ B and negatively regulates inflammatory responses
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Category(English)	Doctoral Thesis
種別(和文)	論文要旨
Type(English)	Summary

論文要旨

THESIS SUMMARY

専攻 : Department of	生命情報	専攻	申請学位 (専攻分野) : Academic Degree Requested	博士 (工学)
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要旨 (英文 800 語程度)

Thesis Summary (approx.800 English Words)

Activation of NF- κ B transcription factor is strictly regulated to prevent excessive inflammatory responses leading to immunopathology. The NF- κ B family is composed of five subunits, p65 (also called RelA), RelB, c-Rel, p50 and p52. In resting cells, I κ B α protein is bound to the p65 and p50 complex and sequesters the complex in the cytoplasm by masking the nuclear localization signals (NLS) of the complex. However, it still remains unclear how NF- κ B activation is negatively controlled. Ubiquitin-protein is a small protein in most eukaryotic organisms and controls many reactions. The PDZ-LIM domain-containing protein PDLIM2 is a nuclear ubiquitin E3 ligase targeting the p65 subunit of NF- κ B for degradation, thus terminating NF- κ B-mediated inflammation.

Using Yeast Two-Hybrid screening, we sought to isolate PDLIM2-interacting seven proteins that are critical for suppressing NF- κ B signaling. Because Yeast Two-Hybrid screening provides eukaryotic system, natural form of proteins, easy to manipulate for finding protein interactions.

Here I identified MKRN2, a RING finger domain-containing protein that belongs to the makorin ring finger protein gene family, as a novel p65 ubiquitin E3 ligase. RING finger domains are composed of eight conserved cysteines (Cys) or histidine (His) residues and are found in several hundred proteins acting as ubiquitin E3 ligases. MKRN2 makes physical interaction with p65 and markedly inhibited p65-induced NF- κ B-mediated transactivation of the reporter in a dose-dependent manner. MKRN2 bound to p65 and promoted the polyubiquitination and proteasome-dependent degradation of p65 through the MKRN2 RING finger domain, thereby suppressing p65-mediated NF- κ B transactivation. MKRN2 shuttles p65 from soluble to insoluble nuclear compartments, where p65 is ultimately degraded by the proteasome. By ubiquitination experiments, MKRN2 promotes polyubiquitination and degradation of p65 through its RING finger domain. I examined whether MKRN2 and PDLIM2 work cooperatively to regulate p65 activation. Knock-down of MKRN2 impaired PDLIM2-mediated p65 polyubiquitination. While the expression of either PDLIM2 or MKRN2 alone minimally decreased p65 protein levels under these conditions, coexpression of PDLIM2 and MKRN2 dramatically decreased p65 protein in the soluble nuclear fraction and increased p65 protein in the insoluble nuclear fraction. Notably, MKRN2 and PDLIM2 synergistically promote polyubiquitination and degradation of p65. Consistently, MKRN2 knockdown in dendritic cells resulted in larger amounts of nuclear p65 and augmented production of proinflammatory cytokines in responses to innate stimuli.

Although, only a few instances of functional dimerization of ubiquitin E3 ligases have been reported, but these results delineate a novel role of MKRN2 in negatively regulating NF- κ B-mediated inflammatory responses, cooperatively with PDLIM2. MKRN2 may not be able to effectively polyubiquitinate p65 in the cytoplasm due to the lack of PDLIM2. Alternatively, polyubiquitination and degradation of p65 itself may occur only in the nucleus, and not in the cytoplasm, even in the presence of MKRN2. Constitutive activation of NF- κ B at sites of inflammation is observed in certain human autoimmune and inflammatory diseases, such as rheumatoid arthritis and bronchial asthma. Thus, the MKRN2-mediated pathway to inhibit p65 activation could be a new molecular target for the treatment of autoimmune and inflammatory diseases.

備考 : 論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1 copy of 800 Words (English).

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