論 文 内 容 の 要 旨
Synopsis of Thesis

〔論文題名 : Thesis Title〕 Akirin2 is critical for inducing inflammatory genes by bridging IκB-ζ and the SWI/SNF complex

(Akirin2はIκBζとSWI/SNF複合体に結合することでマクロファージによる炎症関連遺伝子発現を誘導する)

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〔目 的(Purpose)〕

Innate immune cells such as macrophages sense molecular patterns from microorganisms and damaged cells. These molecular patterns are recognized by several classes of sensor proteins, such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), Nod-like receptors (NLRs) and so on. TLRs and RLRs trigger signaling pathways leading to transcriptional expression of a set of genes involved in inflammation. We previously identified Akirin, a nuclear factor regulating NF-κB dependent transcription in a functional genome-wide RNA-mediated interference (RNAi) screening of *Drosophila* cell culture to isolate new components of the Imd pathway. There are 2 Akirin family members in humans and mice. Akirin2, but not Akirin1 is critical for the production of IL-6 in response to TLR stimuli in mouse embryonic fibroblasts (MEFs) in addition to having a role in mouse development. However, the mechanism of Akirin2 function is not well understood. The objective of our study is to determine the mechanism of action of Akirin2 in macrophages and how Akirin2 controls the TLR-induced transcription of a set of inflammation-related genes.

〔方法ならびに成績(Methods/Results)〕

In the present study, we examined the role of mouse Akirin2 in macrophages by generating a conditional allele. By performing qPCR analysis we found that Akirin2 is essential for the expression of a set of inflammatory genes including *Il6* downstream of TLRs and RLRs. In addition, ELISA and FACS analysis in mice lacking Akirin2 in macrophages show impaired cytokine production in response to *Listeria* infection and clearance of infecting bacteria *in vivo*. Microarray analysis showed that Akirin2-dependent genes tended to exhibit relatively few CpG islands in their promoters. These observations motivated us to examine how Akirin2 regulates inflammatory gene expression. ChIP experiments showed that Akirin2 was directly recruited to its target gene promoters, and was found to control chromatin remodeling by recruiting BAF60 proteins, components of the SWI/SNF complex. Further, by performing coimmunoprecipitation experiments, we identified IκB-ζ as an Akirin2 binding protein via the C-terminal region of Akirin2, and found that IκB-ζ and the NF-κB p50 subunit are required for the recruitment of Akirin2 to the *Il6* promoter. Reciprocally, IκB-ζ was also recruited to the *Il6* promoter in the presence of Akirin2. This study reveals that Akirin2 mediates the physical link between the NF-κB and SWI/SNF complexes, thereby represents a novel paradigm for providing tissue and target specificity for transcription factor interactions with chromatin remodeling machinery.

〔総 括(Conclusion)〕

In summary, this study clearly demonstrates that Akirin2 controls a set of inflammatory genes with non-CpG island promoters by recruiting the SWI/SNF complex and interacting with IκB-ζ. We believe that this is the first study unveiling the mechanism of initiation of chromatin remodeling after NF-κB activation in innate immune cells. Targeting Akirin2 in immune cells might be beneficial for ameliorating inflammatory diseases and may lead to new strategies for combating autoimmune diseases.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

マクロファージなどの自然免疫細胞は病原体の侵入を感知し、IL-6など種々の炎症性サイトカインを産生する。このサイトカイン遺伝子発現にはNF-kBなどの転写因子の活性化や、クロマチンの構造変化が関わっていることが知られている。

申請者は、ショウジョウバエからヒトまで保存され、線維芽細胞においてIL-6の産生に必要であるAkirin2という分子に着目し、マクロファージ特異的にAkirin2を欠損したマウスを作製した。このマウスは細菌感染に対する生体防御応答の低下を認め、また、マクロファージからのIL-6産生が低下していた。その機構として、Akirin2がSWI/SNF複合体およびIkBzと結合することによりクロマチン再構成を制御し、それによりIL-6などのサイトカイン産生を正に制御していることを明らかにした。

本研究成果は、Akirin2が転写因子NF-kBとクロマチン再構成複合体の橋渡しをすることを発見し、サイトカイン産生メカニズムの一端を明らかにしたものであり、炎症制御法の開発にもつながる有用な成果であると考えられる。

以上の点より、本申請者は学位の授与に値するものと考えられる。