

ショウジョウバエにおける新規抗ウイルス dSTING-dIKK β -Relish 経路の発見

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要旨

RNA interference (RNA 干渉) は、昆虫および植物において、主要な抗ウイルス免疫として働く。しかし、これらの生物はウイルス感染によって、何百もの遺伝子群を発現誘導することも知られている。この誘導反応が、どのように抗ウイルス免疫として寄与するのか、その分子機構は不明な部分が多い。今回我々は、ショウジョウバエをモデルとして用い、細菌に対する誘導免疫機構である IMD 経路の一部の因子群、すなわち dIKK β と NF- κ B (Relish) が、抗ウイルス免疫経路に関与することを発見した。この経路の活性化には、STING (ショウジョウバエでは相同遺伝子 dSTING) が関与していた。哺乳類において STING (stimulator of interferon genes) はインターフェロン誘導経路の要であり、ウイルス感染の情報を細胞質内で受け取り、最終的にインターフェロンを発現させる。興味深いことに、無脊椎動物であるショウジョウバエは、このインターフェロン反応を持たない。我々は、dSTING が dIKK β の上流で働き、インターフェロンとは異なる抗ウイルス因子 Nazo (謎) を発現することを見出した。以上の結果から、ショウジョウバエで発見した新規抗ウイルス dSTING-dIKK β -Relish 経路の起源は非常に古く、哺乳類が他の生物から分かれた時、既に機能していたことを示唆する。

文献

Goto A*¹, Okado K*, Martins N, Cai H, Barbier V, Lamiable O, Troxler L, Santiago E, Kuhn L, Paik D, Silverman N, Holleufer A, Hartmann R, Liu J, Peng T, Hoffmann JA, Meignin C, Deaffler L, Imler JL¹. The kinase IKK β regulates a STING and NF- κ B-dependent antiviral response in *Drosophila*. **Immunity** 49:225-234. (2018) * first authors, ¹ Corresponding authors.

Kemp C*, Mueller S*, Goto A, Barbier V, Paro S, Bonnay F, Dostert C, Troxler L, Hetru C, Meignin C, Pfeffer S, Hoffmann JA, Imler JL. Broad RNA Interference-Mediated Antiviral Immunity and Virus-Specific Inducible Responses in *Drosophila*. **J. Immunol.** 190:650-658 (2013)
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Discovery of novel antiviral dSTING-dIKK β -Relish pathway in *Drosophila*

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Abstract

Upon viral infections, insects mainly rely on antiviral RNA interference (RNAi) mechanism, whereas mammalian antiviral innate immunity is predominantly orchestrated by the strong induction of the interferon family. However, analysis of the transcriptome of virus-infected flies revealed deregulated expression of large sets of genes. Some of these changes in gene expression might reflect responses to stress or altered physiology. Interestingly, the IMD pathway have been proposed to play a role in antiviral immunity in *Drosophila*. However, the mechanism of activation of these innate immune signalling pathways in the context of viral infection and the function of the induced genes remain poorly characterized. In this study, we focused on the involvement of the IMD pathway in antiviral immunity.

Unbiased RNAi screen of the IMD pathway in *Drosophila* S2 cells identified that two components of the IMD pathway, the kinase dIKK β and the transcription factor NF- κ B (Relish), were required to control infection by picorna-like viruses. Transcriptome-analyses from both flies and S2 cells identified a set of genes induced by viral infection and regulated by dIKK β and NF- κ B (Relish), which included an ortholog of STING (Stimulator of Interferon genes). Further epistatic analyses showed that dSTING participated in the control of infection by viruses, acting upstream of dIKK β to regulate expression of Nazo, an antiviral factor. Taken together, our data reveal an antiviral function for STING in an animal model devoid of interferons and suggest an evolutionarily ancient role for this molecule in antiviral immunity.

Related publications

Goto A^{*1}, Okado K^{*}, Martins N, Cai H, Barbier V, Lamiable O, Troxler L, Santiago E, Kuhn L, Paik D, Silverman N, Holleufer A, Hartmann R, Liu J, Peng T, Hoffmann JA, Meignin C, Deaffler L, Imler JL¹. The kinase IKK β regulates a STING and NF- κ B-dependent antiviral response in *Drosophila*. **Immunity** 49:225-234. (2018) * first authors, ¹ Corresponding authors.

Kemp C^{*}, Mueller S^{*}, Goto A, Barbier V, Paro S, Bonnay F, Dostert C, Troxler L, Hetru C, Meignin C, Pfeiffer S, Hoffmann JA, Imler JL. Broad RNA Interference-Mediated Antiviral Immunity and Virus-Specific Inducible Responses in *Drosophila*. **J. Immunol.** 190:650-658 (2013)
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