Our body recognizes left-handed RNAs as non-self

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Abstract

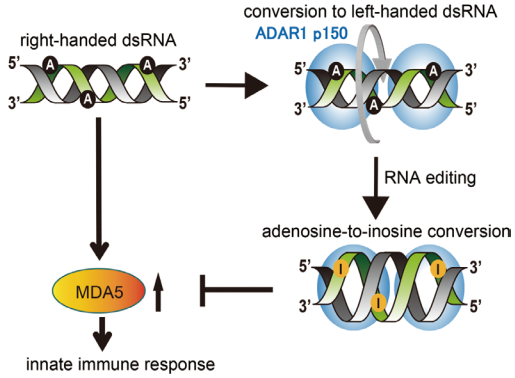
Our bodies are equipped with innate immunity that rapidly detects and eliminates infecting pathogens. Innate immunity recognizes molecular structures common to viruses and other pathogens, including dsRNA structures. However, there is a risk that endogenous dsRNAs are misrecognized as non-self. To avoid this, endogenous dsRNAs are subjected to RNA editing, which converts adenosine to inosine, whereas the detailed mechanism of this RNA editing remains largely unknown. In this study, we found that the RNA-editing enzyme ADAR1 binds to left-handed dsRNAs, which is essential for proper RNA editing. Furthermore, *Adar1* mutant mice, in which ADAR1 cannot bind to left-handed dsRNAs, manifested the symptoms similar to human genetic immune disease. Thus, this study provides an epoch-making achievement that clarified the physiological significance of left-handed dsRNAs.

Background & Results

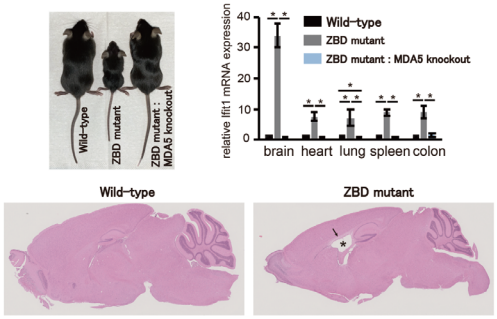
We have clarified that dsRNAs are sensed through its helical structure in vivo. It has been recently revealed that left-handed dsRNAs are also formed in RNA derived from SARS-CoV-2 and influenza viruses. Thus, our findings will be useful for the development of methods for early detection and prevention of viral infection. It is also expected to be applied to safe artificial mRNA synthesis technology, which inhibits unexpected immune responses.

Significance of the research and Future perspective

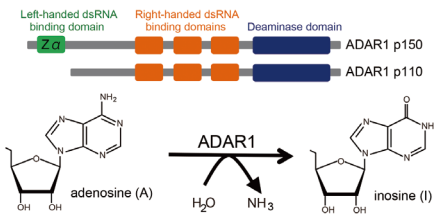
Mammalian genome contains many repeat sequences derived from retrotransposons. When these elements are located on the same RNA, dsRNAs can be formed between repeat sequences. On the other hand, innate immunity senses foreign dsRNA derived from viruses by dsRNA sensor proteins, such as MDA5, and stimulates interferon production. To prevent MDA5 sensing of endogenous dsRNAs as non-self, dsRNAs are subjected to RNA editing, which marks self dsRNAs by inserting inosine. This type of RNA editing is catalyzed by ADAR1, which is consisted of two isoforms: the short ADAR1 p110 and the long ADAR1 p150. We previously reported that ADAR1 p150, but not the p110 isoform, exerts a regulatory function to suppress aberrant activation of innate immunity, whereas the detailed mechanism remains largely unknown. In this study, we focused on the left-handed dsRNA -binding domain termed Zα, which is found only in ADAR1 p150. First, using cultured cells, we found that inserting a mutation in Zα, which abolishes binding ability to left-handed dsRNA, reduced RNA editing efficiency. Then, we generated *Adar1* mutant mice that had the same mutation in Zα and found that they exhibited marked growth retardation and high mortality rate. In these mutant mice, MDA5 was abnormally activated, resulting in overproduction of interferon. *ADAR1* mutations are a cause of Aicardi-Goutières syndrome (AGS), which is characterized by encephalopathy and overproduction of interferon. Of note, the *Adar1* mutant mice developed AGS-like encephalopathy. These results suggest that ADAR1 p150-binding to left-handed dsRNAs is essential for proper RNA editing to prevent aberrant MDA5 activation. In addition, given that mutations in Zα are also found in patients with AGS, these findings suggest that impaired binding to left-handed dsRNA is involved in the pathogenesis of AGS.



ADAR1 p150 binds to left-handed dsRNAs, which is essential for maintaining the proper level of RNA editing at certain sites to prevent aberrant activation of MDA5.



Adar1 mutant mice harboring a point mutation in the Zα domain manifest growth retardation and encephalopathy. MDA5 is aberrantly activated, leading to the increased expression of an interferon-stimulated gene (Ifit1) in various organs.



ADAR1-mediated RNA editing

Patent

Treatise Nakahama, Taisuke; Kawahara, Yukio et al. Mutations in the adenosine deaminase ADAR1 that prevent endogenous Z-RNA binding induce Aicardi-Goutières-syndrome-like encephalopathy. Immunity. 2021, 54(9), p.1976-1988, doi: 10.1016/j.immuni.2021.08.022

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Keyword RNA editing, AGS, Z-RNA, autoimmune disease, interferon