Adenosine to inosine RNA editing in animal cells

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Abstract

Major advances in the understanding of adenosine deaminases acting on RNA (ADARs) have come from the generation of *ADAR* mutant animals. In mice, *ADAR1* is a widely expressed essential gene and loss of function in embryos leads to apoptosis through unknown mechanisms in many different cell types. Mammalian *ADAR2* is required primarily to edit glutamate receptor transcripts in the nervous system. The *Drosophila melanogaster* genome contains one *Adar* gene; mutant flies are normal in morphology and lifespan, but severely compromised neurologically and behaviourally. In *C. elegans*, double mutants in *Adr1* and *Adr2* genes are viable with chemosensory defects that appear to arise from interactions between RNA editing and RNA interference. ADARs also extensively deaminate long double-stranded (ds) RNA in a process that has been proposed to have antiviral effects. Genome sequences have facilitated progress in identifying edited RNAs. The majority of the twenty-three edited transcripts identified in *Drosophila* encode proteins involved in rapid chemical and electrical neurotransmission and extensive editing of embedded *Alu* RNAs has been found.

1 Introduction: ADAR RNA editing in vertebrates

ADARs (Fig. 1) were first discovered in *Xenopus laevis*. Early efforts to extend antisense RNA injection experiments in oocytes with later injections to silence maternal transcripts expressed in activated eggs failed to produce gene silencing. It was found that silencing in activated eggs failed because the double-stranded (ds)RNA intermediate formed by pairing of the injected antisense RNA with the target transcript was unstable (Bass and Weintraub 1987; Rebagliati and Melton 1987). The instability was due to an activity released from the nucleus at germinal vesicle breakdown when the oocyte completes meiosis.

When these experiments were conducted it was thought that stable dsRNA would produce silencing by inhibiting translation. The enzyme responsible was thought to have prevented silencing by an apparent helicase-like action that led to separation of RNA strands. The released target RNA was assumed to be still translatable. Further work showed that the resulting single-stranded (ss)RNA was altered and did not reanneal due to conversion of up to half of the adenosines in

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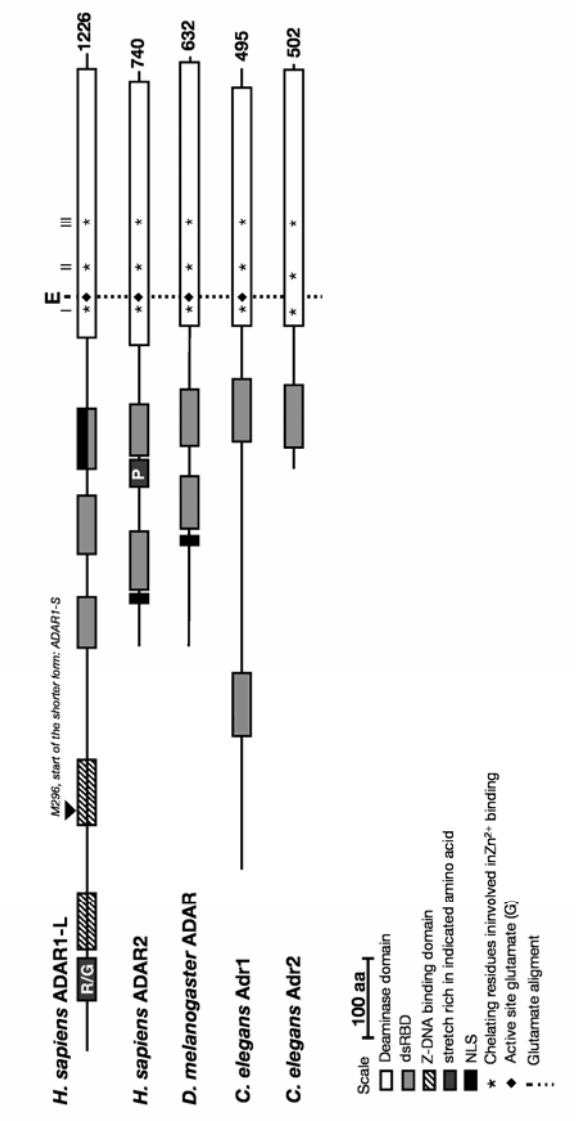

Fig. 1. Structures of ADAR genes from animal model organisms. Deaminase domains, double-stranded RNA binding domains (dsRBDs), and Z-DNA-binding domains are indicated. The glutamate in the deaminase active site is labelled E and the motifs in the deaminase domain that chelate zinc in the active site are labelled I to III.

dsRNA to inosine by an adenosine deaminase acting on RNA (ADAR) (Bass and Weintraub 1988). Inosine forms only one hydrogen bond with uracil, weakening the RNA strand pairing (Fig. 2B).