LETTER

Is the p150 isoform of the RNA editing enzyme Adenosine Deaminase 1 really responsible for embryonic lethality?

We read with interest the manuscript by Ward et al. (1) in PNAS in which selective disruption of the p150 isoform, but not the p110 isoform, of the RNA editing enzyme Adenosine Deaminase 1 (ADAR1) was reported to cause early embryonic lethality.

ADAR1 exists in two molecular weight isoforms: a long protein of 150 kDa (p150), which is expressed from an interferon-inducible promoter using a translational start site in exon 1A, and a short form of 110 kDa (p110), which is expressed from two constitutive promoters using exon 1B or 1C and an alternative translational start site in exon 2. Both isoforms have the ability to change gene expression by converting adenosine to inosine at specific sites in RNA, thus altering protein structure through the subsequent readout of inosine as guanosine during translation.

Simultaneous deletion of the two isoforms of ADAR1 has previously been shown to cause embryonic lethality attributable to failure of the hematopoietic system during early development between embryonic day (E) 11.5 and E12.5 (2). Although these investigations did not shed light on whether one or both isoforms were responsible, it is known that the inducible p150 isoform is not detectable at the mRNA or protein level at E10.5 and is detectable only weakly at E15, whereas the p110 isoform is expressed at both of these stages (3), suggesting that the latter may be more important for the effects on hematopoiesis.

Surprisingly, Ward et al. (1) reported that specific disruption of the inducible p150 isoform, by removal of exon 1A, is embryonic lethal at an early stage, identical to the effects of the double deletion. They claimed that production of the p110 isoform is unaffected because mRNA for the p110-specific exon 1B is still present (figure 1E of ref. 1). However it is well known that the presence of a strong promoter, such as phosphoglycerate kinase in the selection cassette, located in an intron can interfere with transcription, resulting in a hypomorph in which mRNA levels can be reduced by as much as 90% (e.g., ref. 4). It is possible therefore that mRNA expression for p110 in the p150-deleted mice, although present, is also severely reduced, resulting in down-regulation of p110 protein. Unfortunately, Ward et al. (1) did not show whether p110 protein is actually expressed in these mice. Without such a demonstration, it is possible that the targeting strategy has simply produced another functional double deletion.

We believe therefore that until a full complement of p110 protein can be shown in the p150-deleted mice, the conclusion that the p150 isoform of ADAR1 is required for embryogenesis must remain controversial.

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The authors declare no conflict of interest.

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