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ADAR1, the guardian to the innate immune response

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Adenosine deaminase acting on RNA (ADAR) can convert adenosine to inosine in double-stranded (ds) RNA and this is referred to as RNA editing. Inosine in RNA can be read as guanosine so the deamination by ADAR enzymes can result in recoding, with another amino acid being inserted into the protein at the edited position. However, the main function of ADAR1 in mammals is not recoding but prevent activation of the innate immune sensors by cellular dsRNA. Inosine in transcripts helps the cell distinguish them from viral or pathogenic dsRNA, acting similar to a bar-code, the cell can recognize endogenous dsRNA. DsRNA containing inosine binds to and prevents activation of the melanoma differentiation-associated protein 5 (MDA5) dsRNA sensor.

ADAR1 has two main isoforms, ADAR1 p110 that is mainly nuclear and ADAR1 p150 that is induced by interferon and is predominantly cytoplasmic though both isoforms can shuttle. When ADAR1 is induced by interferon during a viral response, it edits all the dsRNA that is present in the cytoplasm, both cellular and viral dsRNA, as its main function is to turn off the innate immune response. Therefore, the cellular location of ADAR1 is crucial for its biological role.

ADAR1 also has editing independent functions that prevents activation of the immune response. It can inhibit activation of Protein Kinase R (PKR) by a direct protein-protein interaction between its dsRBDIII and the kinase domain of PKR, this interaction does not require RNA editing activity but requires both enzymes to be bound on dsRNA.