ADAR (Adenosine Deaminase Acting on RNA) is a family of enzymes that catalyze the conversion of adenosine (A) to inosine (I) in double-stranded RNA (dsRNA) through a process known as **RNA editing**. This post-transcriptional modification alters RNA sequences, affecting gene expression, splicing, RNA stability, and translation.

Types of ADAR Enzymes 1. **ADAR1**:

1. Ubiquitously expressed with two isoforms:
   1. **p150**: Induced by interferons and predominantly cytoplasmic.
   2. **p110**: Constitutively expressed and localized in the nucleus.
2. Plays a crucial role in innate immunity by modifying endogenous dsRNA to prevent inappropriate activation of immune sensors like MDA5.

2. **ADAR2**:

1. Primarily expressed in the brain and essential for editing transcripts related to neurotransmission and neuronal function.
2. Key substrate: **GRIA2** mRNA, encoding a subunit of the AMPA receptor, where editing impacts calcium permeability.

3. **ADAR3**:

1. Found mainly in the brain but has no known enzymatic activity. Its role may involve modulating ADAR1 and ADAR2 activity.

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Functions of ADAR 1. **RNA Editing**:

1. Inosine is read as guanosine by the translational machinery, leading to changes in the encoded protein.
2. Critical substrates include:
   1. **GRIA2 (glutamate receptor)**: Affects calcium ion flow in neurons.
   2. **GABRA3 (GABA receptor)**: Impacts inhibitory neurotransmission.

2. **Innate Immunity Regulation**:

1. ADAR1 prevents immune sensors like **MDA5** and **PKR** from recognizing self-dsRNA, thus avoiding autoimmunity.

3. **Transcriptome Diversification**:

1. Editing expands the functional repertoire of proteins and fine-tunes gene expression.

4. **Role in Development and Survival**:

1. ADAR1 is essential for embryonic development and immune homeostasis.

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ADAR in Diseases 1. **Cancer**:

1. Dysregulation of ADAR1 is associated with tumor progression and immune evasion:
   1. Overexpression of ADAR1 can promote editing of transcripts that favor cell survival and

metastasis.
2. ADAR1 contributes to resistance to immune checkpoint inhibitors by editing dsRNA and evading immune activation.

2. **Neurological Disorders**:

1. Mutations or dysregulation in ADAR2-mediated editing (e.g., GRIA2 transcript) are linked to diseases like epilepsy, ALS, and schizophrenia.

3. **Autoimmune Diseases**:

1. Loss of ADAR1 activity can lead to aberrant recognition of self-dsRNA by innate immune sensors, causing autoinflammatory conditions such as Aicardi-Goutières syndrome.

4. **Viral Infections**:

1. ADAR1 can edit viral RNA, influencing viral replication and immune recognition.

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Therapeutic Potential of ADAR 1. **Gene Editing Tools**:

1. Harnessing ADAR's ability to edit RNA for precise therapeutic modifications (e.g., correcting mutations at the RNA level).
2. Engineered ADAR systems, such as **REPAIR (RNA Editing for Programmable A-to-I Replacement)**, are under investigation.

2. **Targeting ADAR1 in Cancer**:

1. Inhibiting ADAR1 to enhance immune recognition of tumor cells is a promising immunotherapeutic strategy.

3. **Restoring Normal Editing in Neurological Disorders**:

1. Therapeutic approaches aim to correct or restore ADAR2-mediated editing in diseases like ALS.

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Research Directions 1. Understanding the balance between beneficial and detrimental RNA editing by ADARs in cancer and immunity. 2. Development of small-molecule modulators or gene therapies targeting ADARs. 3. Exploring ADAR as a diagnostic and prognostic biomarker in various diseases.