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QUESTION

Relate splicing events to diseases like cancer, neurological disorders, or genetic diseases caused by splicing mutation

How might errors in splicing lead to change in gene expression or disease?

ANSWER

Errors in Splicing: Molecular Mechanisms and Disease Implications

Introduction to RNA Splicing

RNA splicing is a pivotal process in eukaryotic gene expression that removes non-coding introns from pre-mRNA and ligates coding exons to form mature mRNA. This process, facilitated by the spliceosome, is tightly regulated to ensure accurate protein synthesis. Splicing errors, however, can disrupt gene expression, leading to profound cellular and systemic consequences, including disease development.

Mechanisms Behind Splicing Errors

1. Mutations in Splice Sites:

The conserved sequences at the 5’ donor site, 3’ acceptor site, and branch point are important for spliceosome recognition. Point mutations in these regions can:

- **Skip exons**: The spliceosome bypasses exons, resulting in truncated proteins.

For example:Duchenne Muscular Dystrophy: Exon skipping in the DMD gene results in a defective dystrophin protein

- **Retain introns:** Introns are erroneously included, introducing non-coding sequences into the mRNA.
- **Activate cryptic splice sites**: Mutations may lead to splicing at unintended sites, producing aberrant transcripts.

2. Dysregulation of Splicing Factors:

Splicing factors (e.g., SR proteins, hnRNPs) direct exon recognition and spliceosome assembly. Mutations or misregulation of these proteins can alter exon inclusion or exclusion patterns.

- **Example:** SF3B1 mutations, prevalent in myelodysplastic syndromes, lead to aberrant splicing of transcripts involved in hematopoiesis.

3. Epigenetic and Environmental Influences:

Chromatin structure and histone modifications (e.g., H3K36me3) can influence spliceosome recruitment. Environmental stressors, such as oxidative stress, may also disrupt normal splicing patterns.

MOLECULAR CONSEQUENCES OF SPLICING ERRORS

1. Aberrant Protein Products: Protein Dysfunction and Loss of Function

Splicing errors can generate mRNA with premature termination codons, resulting in truncated or dysfunctional proteins. These proteins may interfere with normal cellular processes or gain toxic functions.

- **Truncated Proteins**: Errors may introduce premature stop codons, leading to non-functional or unstable proteins.
- **Gain of Toxic Function**: Mis-spliced proteins can gain harmful properties, interfering with normal cellular activities.

2. Disruption of Isoform Balance:

Alternative splicing generates protein isoforms with distinct functions. Mis-splicing can alter isoform ratios, shifting cellular pathways.

- **Example:** The pro-apoptotic and anti-apoptotic isoforms of BCL-X are regulated by alternative splicing; errors here contribute to cancer progression.

3. Nonsense-Mediated Decay (NMD):

Erroneous transcripts are often targeted for degradation by NMD. While protective, excessive degradation can deplete essential proteins, exacerbating disease phenotypes.

DISEASES ASSOCIATED WITH SPLICING ERRORS

1. Cancer

Splicing errors are a hallmark of many cancers, as they disrupt the balance between oncogenes and tumor suppressor genes.

Mechanisms:

- **Activation of Oncogenes**: Splicing mutations can produce oncogenic isoforms that promote cell proliferation and survival.
- **Inactivation of Tumor Suppressors**: Aberrant splicing of tumor suppressor genes can impair their function, removing critical regulatory checkpoints.

Examples:

- **SF3B1 Mutations**: Found in chronic lymphocytic leukemia (CLL), breast cancer, and uveal melanoma. These mutations alter splice site recognition, leading to aberrant splicing of genes involved in chromatin remodeling (e.g., BRD9) and mitochondrial metabolism (e.g., ABCB7).
- **BCL2 Isoform Shift:** Alternative splicing of the BCL2 gene produces anti-apoptotic isoforms, enhancing cancer cell survival.
- **TP53 Splicing Errors:** Mutations affecting TP53 splicing generate truncated p53 proteins, disabling its tumor-suppressive functions.

2. Neurological Disorders

Precise splicing is critical for neuronal development and function. Disruptions in splicing lead to impaired neuronal signaling, neurodegeneration, or developmental abnormalities.

Examples:

- **Spinal Muscular Atrophy (SMA):**
  Caused by mutations in the SMN1 gene, leading to defective splicing of SMN2. This results in reduced levels of survival motor neuron (SMN) protein, critical for motor neuron health, causing progressive muscle weakness and atrophy.
- **Amyotrophic Lateral Sclerosis (ALS):**
  Mutations in splicing-related genes like FUS and TDP-43 lead to mis-splicing of critical neuronal genes, contributing to motor neuron degeneration.

- **Frontotemporal Dementia:**
  Mis-splicing of the MAPT gene, encoding tau protein, leads to accumulation of pathological tau isoforms.

3. Genetic Disorders

Mutations affecting splicing often underlie hereditary diseases by disrupting the production of functional proteins.

Examples:

- **β-Thalassemia**:
  Mutations in the β-globin gene (HBB) lead to defective splicing, causing reduced hemoglobin production. This results in anemia, fatigue, and other complications.
- **Cystic Fibrosis:**
  Splicing mutations in the CFTR gene (e.g., intron retention) reduce the production of functional CFTR protein, leading to thick mucus accumulation in the lungs and other tissues.
- **Duchenne Muscular Dystrophy (DMD):**
  Splicing mutations in the dystrophin gene produce truncated, non-functional dystrophin proteins, leading to progressive muscle degeneration.

MOLECULAR INSIGHTS AND ADVANCES

1. Spliceosome Mutations:

Mutations in U2AF1 and SRSF2 destabilize splice site recognition, shifting splicing fidelity.

- **Example**: U2AF1 mutations preferentially affect 3’ splice sites with weaker pyrimidine tracts, altering exon inclusion in key metabolic genes.

2. Cryptic Splice Sites:

Mutations can activate nearby cryptic splice sites, competing with canonical sites.

- **Example:** Cryptic splicing in BRCA1 leads to loss of tumor-suppressor function, predisposing individuals to breast and ovarian cancer.