Pediatrics & Therapeutics
ISSN: 2161-0665

Uckun, Pediatr Therapeut 2011, 1:1
DOI: 10.4172/2161-0665.1000e101

Editorial Open Access

Role of Defective RNA Processing in the Pathogenesis of Pediatric Diseases

Fatih M. Uckun*

Fatih M. Uckun, Professor of Pediatrics, University of Southern California Keck School of Medicine, USA

The nuclear synthesis of mature messenger RNA (mRNA) from precursor mRNA (pre-mRNA), the primary transcript generated from the genomic DNA, is initiated by the recruitment of specific spicing regulators via adaptor complexes and assembly of a pre-spliceosome on the target nascent pre-mRNA. It requires a coordinated cotranscriptional and posttranscriptional pre-mRNA processing and splicing for noncoding intron removal along with a concerted action of several transcription factors and RNA polymerase II elongation complex. Canonical splicing of pre-mRNAs usually involves 2 trans-esterification reactions mediated by a catalytically active spliceosome, the major element of the splicing machinery, that undergoes a dynamic multistep assembly, rearrangement and catalytic site remodeling for its activation [1-3]. Spliceosome as an evolutionarily conserved unique mixed protein/RNA enzyme is a macromolecular ribonucleoprotein (RNP) complex that displays a dramatic structural and compositional dynamics with massive remodeling of its RNP subunits. Spliceosome contains as its major building blocks at distinct stages of its stepwise assembly varying combinations of uridine-rich small nuclear RNP particles (snRNPs) U1, U2, U5, and U4/U6 as well as several non-snRNP proteins [1-3]. It has been shown that the spliceosome rearrangements and exon ligation incorporate proofreading steps to ensure a high of fidelity in splicing catalysis [4].

While during constitutive splicing the target exons are recognized by the splicing machinery and included in the mature mRNA, exons are not always recognized and sometimes excluded in the mature mRNA during the splicing modes known as alternative splicing, including exon skipping, intron retention, alternative splice-site activation, and mutually exclusive splicing. Alternative pre-mRNA splicing is a mechanism by which varying isoforms of mature mRNAs (and thus multiple protein isoforms) are generated from the same gene [5-7]. Alternative splicing events and their regulators can be identified transcriptome-wide with high resolution diagnostic assay platforms, including splice-sensitive high-density microarrays/alternative splicing microarray profiling, exon junction microarrays, deep-transcriptome sequencing and high-throughput DNA sequencing [8,9]. Deep sequencing studies have revealed that more than 90% of human genes undergo alternative splicing [5-9]. Alternative splicing provides the foundation for the proteomic complexity and it is intimately linked to lineage specification and differentiation of mammalian cells. An average of 7-10 mRNAs are generated from each pre-mRNA and in human cells, more than 100,000 proteins are generated from approximately 20,000 open reading frames [1].

Alternative splicing is regulated by (i) both intron- or exon-associated conserved short cis-acting RNA sequence elements known as by splicing enhancers (intronic splicing enhancers, ISE and exonic splicing enhancers, ESE) and silencers (intronic splicing silencers, ISS and exonic splicing silencers, ESS) that modulate the splice site use via binding to transacting regulatory proteins (repressors and activators), (ii) the pre-mRNA secondary structure affected by multiple factors including intronic and exonic mutations, (iii) the rate of RNA synthesis and elongation of RNA polymerase II, (iv) expression levels and function of splicing factors, (v) nucleosome positioning and density at alternative splice sites, as well as (vi) epigenetically by chromatin structure and histone modifications well as expression levels of chromating remodeling complexes such as the ATPase-dependent SWI/SNF subunit of BRM [6-8]. Among the transacting regulators, the serine/arginine-rich "SR" proteins generally promote the recruitment of the splicing machinery to the splice sites, whereas the heterogeneous nuclear RNP (hnRNP) particle proteins (e.g hnRNPA1 and polypyrimidine tract binding protein/PTB) act as splicing repressors by reducing the efficiency of splice junction recognition. Non-coding RNAs affect chromatin structure and may participate in regulation of alternative splicing.

Corruption of the alternative splicing mechanism has been implicated in the pathogenesis of various debilitating pediatric illnesses, including retinitis pigmentosa causing blindness, Frasier syndrome causing urogenital disorders and gonad developmental defects, cystic fibrosis, spinal muscular atrophy, infant leukemia, and pediatric acute lymphoblastic leukemia (ALL), the most common form of childhood cancer [10-17]. Aberrant splicing appears to be particularly common in ALL and involves several regulatory genes that determine the fate of leukemia cells exposed to chemotherapy or radiation therapy [12-17]. The most commonly observed aberrations involve the chromatin remodeling protein IKAROS [13,14] and the inhibitory lymphoid lineage signaling molecule CD22 [12].

Recent discoveries regarding the molecular regulatory mechanisms governing RNA processing, alternative splicing, and pleiotropic functional profiles of splicing proteins may provide the foundation for therapeutic innovation against difficult to treat diseases associated with aberrant RNA processing or inappropriately amplified expression of specific gene products. For example, spliceosome mediated RNA transsplicing can potentially replace an aberrant transcript with a wildtype sequence [7,18]. The *trans*-splicing process is induced by engineered 'RNA *trans*-splicing molecules', which target a selected pre-mRNA to be reprogrammed via two complementary binding domains. The unique ability of U1snRNP bound to the last exon to promote mRNA degradation can be used to design gene silencing strategies using synthetic bifunctional oligonucleotides known as U1 adaptors that contain a target domain complementary to a site in the target gene's last exon and a U1 domain for recruitment of U1snRNP

***Corresponding author:** Fatih M. Uckun, Professor of Pediatrics, University of Southern California Keck School of Medicine, Head, Translational Research in Leukemia and Lymphoma, Children's Center for Cancer and Blood Diseases, CHLA, Los Angeles, CA, USA, E-mail: uckun@usc.edu

Received September 08, 2011; **Accepted** October 18, 2011; **Published** October 20, 2011

Citation: Uckun FM (2011) Role of Defective RNA Processing in the Pathogenesis of Pediatric Diseases. Pediatr Therapeut 1:e101. doi:10.4172/2161-0665.1000e101

via base-pair interaction with the U1 small nuclear RNA component [7,19]. It has been shown that tethering of U1 snRNP to the target pre-mRNA using U1 adaptors inhibits poly(A)-tail addition and promotes degradation [19]. Advances in the nanotechnology field provide a unique opportunity to selectively deliver appropriately designed antisense oligonucleotides or chimeric molecules for exon-specific splicing enhancement to therapy-refractory leukemia cells by using multifunctional nanoparticles made of biodegradable block copolymers of polyethyleneglycol and cationic polycarbonate [20].

Ackowledgments

F.M.U is supported by DHHS/NIH grants U01-CA-151837, R01-CA-154471, and a V Foundation Translational Research Grant.

References

1. Hofmann JC, Husedzinovic A, Gruss OJ (2010) The function of spliceosome components in mitosis. Nucleus 1: 447-459.
2. Wahl MC, Will CL, Lührmann R (2009) Thespliceosome: Design principles of a dynamic RNP machine. Cell 136: 701-718.
3. Rino J, Carmo-Fonseca M (2009) Thespliceosome: a self-organizedmacromolecular machine in the nucleus. Trends Cell Biol19: 375-384.
4. Mayas RM, Maita H, Staley JP (2006) Exon ligaion is proof read by the DExD/H-box ATPase Prp22p. Nat StructMol Bio 13: 482-490.
5. Fackenthal JD, Godley LA (2008) Aberrant RNA splicing and its functional consequence in cancer cells. Dis Model Mech 1: 37-42.
6. Luco RF, Allo M, Schor IE, Kornblihtt AR, Misteli T (2011)Epigenetics in Alternative Pre-mRNA Splicing. Cell 144: 16-26.
7. Buratti E, Baralle D (2010) Novel roles of U1 snRNP in alternative splicing regulation. RNA Biol 7:412-419.
8. David CJ, Manley JL (2008) The search for alternative splicing regulators: new approaches offer a path to a splicing code. Genes Dev 22: 279-285.
9. Pan Q, Shai O, Lee LJ, Frey BJ, Blencowe BJ (2008) Deep surveying of alternative splicing complexity in the human transcriptomeby high-throughput sequencing. Nat Genet 40: 1413-1415.
10. Faustino NA, Cooper TA (2003) Pre-mRNA splicing and human disease. Genes Dev 17:419 –437.
11. Venables JP, Klinck R, Koh C, Gervais-Bird J, Bramard A, et al.(2009) Cancer-associated regulation of alternative splicing. Nat StructMolBiol16: 670-675.
12. Uckun FM, Goodman P, Ma H, Dibirdik I, Qazi S (2010) CD22 Exon 12 Deletion as a Novel Pathogenic Mechanism of Human B-Precursor Leukemia. ProcNatlAcadSci USA107:16852-16857.
13. Sun L, Goodman PA, Wood CM, Crotty ML, SenselM , et al. (1999) Expression of aberrantly spliced oncogenic ikaros isoforms in childhood acute lymphoblastic leukemia. J ClinOncol17: 3753-3766.
14. Sun L, Heerema N, Crotty L, Wu X, Navara C, et al. (1999) Expression of dominant-negative and mutant isoforms of the antileukemic transcription factor Ikaros in infant acute lymphoblastic leukemia. ProcNatlAcadSci U S A. 96: 680-685.
15. Goodman PA, Wood CM, Vassilev A, Mao C, Uckun FM. (2001) Spleen tyrosine kinase (Syk) deficiency in childhood pro-B cell acute lymphoblastic leukemia. Oncogene. 20: 3969-3978.
16. Wood CM, Goodman PA, Vassilev AO, Uckun FM (2003) CD95 (APO-1/FAS) deficiency in infant acute lymphoblastic leukemia: detection of novel soluble Fas splice variants. Eur J Haematol70: 156-171.
17. Goodman PA, Wood CM, Vassilev AO, Mao C, Uckun FM (2003) Defective expression of Bruton's tyrosine kinase in acute lymphoblastic leukemia. Leuk Lymphoma44: 1011-1018.
18. Liu X, Jiang Q, Mansfield SG, Puttaraju M, Zhang Y , et al. (2002) Partial correction of endogenous DF508 CFTR in human cystic fibrosis airway epithelia by spliceosome-mediated RNA trans-splicing. Nat Biotechnol20: 47-52.
19. Goraczniak R, Behlke MA, Gunderson SI (2009) Gene silencing by synthetic U1 adaptors. Nat Biotechnol27:257-263.
20. Ong ZY, Fukushima K, Coady DJ, Yang YY, Ee PL, et al. (2011) Rational design of biodegradable cationic polycarbonates for gene delivery. J Control Release 152: 120-126.