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TOPIC HIGHLIGHT

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Alternative splicing of DNA damage response genes and gastrointestinal cancers

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Abstract

Alternative splicing, which is a common phenomenon in mammalian genomes, is a fundamental process of gene regulation and contributes to great protein diversity. Alternative splicing events not only occur in the normal gene regulation process but are also closely related to certain diseases including cancer. In this review, we briefly demonstrate the concept of alternative splicing and DNA damage and describe the association of alternative splicing and cancer pathogenesis, focusing on the potential relationship of alternative splicing, DNA damage, and gastrointestinal cancers. We will also discuss whether alternative splicing leads to genetic instability, which is considered to be a driving force for tumorigenesis. Better understanding of the role and mechanism of alternative splicing in tumorigenesis may provide new directions for future cancer studies.

Key words: Alternative splicing; DNA damage; Gastrointestinal cancer; Mutation; Genetic instability

Core tip: Alternative splicing is a fundamental process of gene regulation in eukaryotes. Alternative splicing of DNA damage repair proteins is a significant cause of gene mutations, and those mutations in turn affect alternative splicing in cancer. Alternative splicing is associated with tumorigenesis by contributing to genetic instability. Therefore, alternative splicing of DNA damage response-related genes has an important role in tumorigenesis, survival, and growth of gastrointestinal cancers. In summary, the alternative splicing variants of these genes could be potential targets for both diagnosis and treatment of gastrointestinal cancers.

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INTRODUCTION

Alternative splicing is a fundamental process of gene regulation, which results in a single gene that codes for multiple proteins by excluding and/or including particular exons from pre-mRNA produced from that gene[1]. The process is performed by the spliceosome composed of five small nuclear ribonucleoproteins (snRNPs; U1, U2, U4, U5, and U6) and more than 100 different polypeptides[2]. In this process, many different types of proteins are translated from mRNA of the same gene origin and contribute to protein diversity. For example, at least 60% of human gene products undergo alternative splicing[3], approximately 100000 alternative splicing events have been identified in the human genome, and up to 95% of human multi-exonic genes have been alternatively spliced[4]. There are approximately 20000-35000 protein-

coding genes in a mammalian genome[5], but the number of proteins generated by alternative splicing is much higher[6] because many of these genes have multiple splicing patterns compensate up to thousands[7]. Thus, alternative splicing is a common phenomenon in the process of mammalian gene regulation and generation of protein diversity.

DISTURBED ALTERNATIVE SPLICING IN HUMAN DISEASES

Alternative splicing events may occur in both normal and disease-related gene regulation processes. The frequency of alternative splicing is higher in cancerous tissues than in normal tissues[8]. Occasionally, alternative splicing variants are expressed in cancer cells but not in normal cells. For example, far upstream element-binding protein (FBP)-interacting repressor (FIR) splice variants lacking or containing exon 2 and/or exon 5 are expressed in the majority of hepatocellular carcinomas (HCCs) but not in normal hepatocytes[9]. A well-known tumor suppressor gene p53 is alternatively spliced to produce at least twelve protein isoforms, which have important roles in cancer formation and progression[10]. It has been suggested that missense or silent mutations affect splicing[11-15]. According to the human gene mutation database, approximately 84% of hereditary diseases are associated with point mutations[16]. Teraoka *et al*[17] suggested that 48% of these mutations result in defective splicing in the ATM gene in patients with ataxia-telangiectasia, and ATM has also been reported to be alternatively spliced in several types of cancer[18-20]. López-Bigas *et al*[11] estimated that more than 60% of all human disease-related mutations affect splicing. Lim *et al*[21] suggested that 22% of disease alleles that were originally classified as missense mutations may also affect splicing and approximately one third of all disease-causing mutations alter pre-mRNA splicing. Alternative splicing variants of many genes and some well-known splicing factors have been reported to be associated with numerous cancers. For example, Ikaros family genes include Ikaros, Helios, and Aiolos. The Ikaros gene (*ZNFN1A1*) is a member of the Kruppel transcription factor family characterized by the presence of zinc-finger domains located at their N- and C-termini and is alternatively spliced to give a number of variants[22]. Ikaros itself acts as a tumor suppressor in the lymphoid lineage[23], but alternative splicing variants, such as Ik11, are aberrantly expressed in B-cell lymphoproliferative disorders and involved in tumor pathogenesis[24]. Helios was found to be abnormally spliced in adult T-cell leukemia, and deregulation of Helios expression promotes T-cell growth[25]. The splicing factor SRSF6 is an oncoprotein reported to be over-expressed in lung and colon cancers[26]. Another splicing factor hnRNP has been suggested to be an oncogenic driver in glioblastoma[27,28]. Recurrent somatic mutations of splicing machinery genes, such as SF3B1, U2AF1, ZRSR2, and SRSF2, have been reported in numerous malignancies, including myelodysplastic syndromes, leukemias, and ovarian and gastric cancers[29-33]. Pre-mRNA processing factor 6 (PRPF6), a member of the tri-snRNP spliceosome complex, is required for alternative splicing of a number of genes, including ZAK kinase, and splicing activity of PRPF6 is important for colon cancer cell growth[34,35]. In addition to the associations shown in the above examples, many studies have suggested that alternative splicing is indeed closely related to certain diseases such as gastrointestinal cancers[18,36-48].

ABERRANT SPLICING OF DNA DAMAGE REPAIR GENES CAUSES GASTROINTESTINAL CANCERS

Impaired DNA damage responses induce genetic instability. DNA double-stranded breaks represent one of the most severe types of DNA damage and promote genetic instability that is lethal to cells if left unrepaired[49,50]. Genetic instability includes two major categories: one is microsatellite instability, which involves subtle changes in DNA sequences (faulty DNA repair), and the other is chromosomal instability (CIN), which is characterized by gains and losses of whole or parts of chromosomes, and CIN is considered to be a driving force for tumorigenesis[51,52]. Single-stranded or double-stranded DNA breaks increase the susceptibility of chromosomal gross structural alterations that lead to CIN[51]. CIN is closely associated with the intrinsic multidrug resistance of cancer[51,53]. The possible association of DNA damage, alternative splicing, and genetic instability is schematically shown in Figure 1.

Chromosomal alterations are found in nearly all human cancers[54]. As mentioned above, severe types of DNA damage promote genetic instability and are an integral component of human neoplasia[55]. Alternative splicing affects the stability of transcripts by introducing premature STOP codons and directing mRNA degradation through the nonsense-mediated mRNA decay pathway[56]. Alternative splicing of DNA damage response genes promotes genetic instability. Therefore, alternative splicing is closely associated with DNA damage and tumorigenesis. Previous studies have shown that gastrointestinal cancers are closely associated with alternative splicing of DNA damage-related genes that cause genetic instability. For example, ATM is involved in the homologous recombination (HR) pathway of DNA repair, and MRE11 is a component of the DNA damage sensor MRN; these genes are found to be alternatively spliced in colon cancer cells[18,36]. Germline mutations in the DNA mismatch repair genes, *MSH2*, *MLH1*, *MSH6* and *PMS2*, are the cause of colon cancer, called Lynch syndrome[44,45] and they are reported to be spliced in a number of gastrointestinal cancers[37-39,57]. Splicing factor 3b (SF3b) is a subcomplex of the U2 snRNP in the spliceosome[58]. SAP155 (a subunit of SF3b) is required for proper FIR expression and *vice versa*, and SAP155 knockdown or SF3b inhibition disrupts alternative splicing of FIR pre-mRNA and

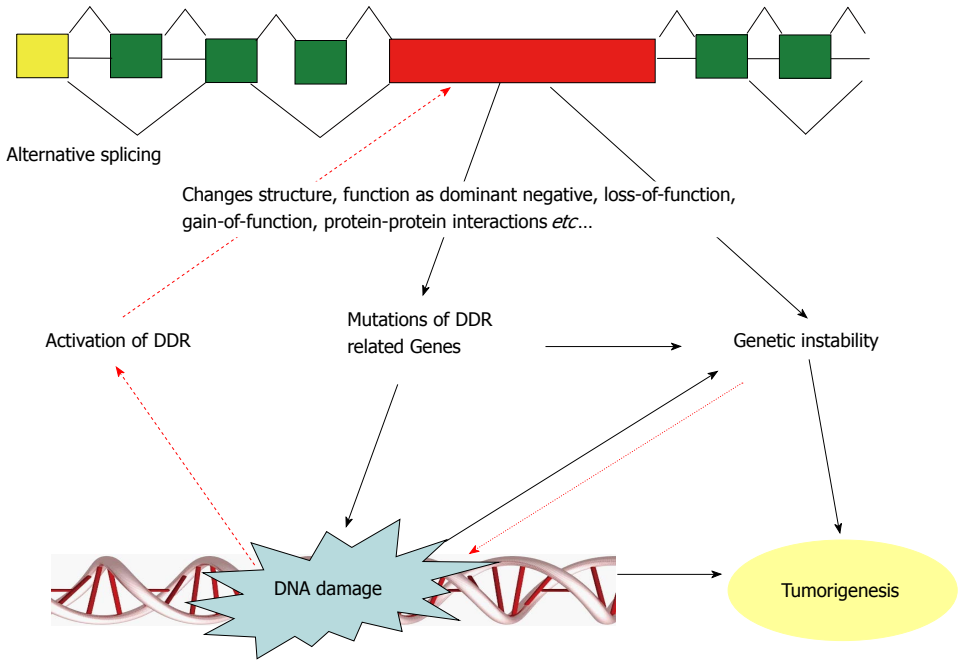

Figure 1 Schematic view of the possible connection between alternative splicing and DNA damage. When DNA damage occurs, DNA damage response (DDR) is activated, which then activates alternative splicing that leads to mutations and splicing alteration of DDR-related genes. This process leads to the accumulation of DNA damage. DNA damage is a major cause of genetic instability. On the other hand, alternative splicing directly or indirectly causes genetic instability *via* mutations of related genes including DDR-related genes. Genetic instability is one of the major causes of tumorigenesis.

generates FIRΔexon2[59]. FIR also acts as a molecular sensor for bleomycin-induced DNA damage by potentially interacting with DNA-PKcs and Ku-86/XRCC5[60] and has been reported to be alternatively spliced in colorectal cancer[40] as well as in HCCs[9]. Multifunctional splicing factor U2AF65, which has biotinylated triplex DNA affinity, has been reported to be associated with colorectal cancers[61]. Poly (ADP-ribose) polymerase (PARP)-1 is involved in single- stranded DNA damage repair and has a control role in the HR pathway[62]. PARP-1 is activated by *Helicobacter pylori* in the development and proliferation of gastric cancer[63]. The tumor suppressor genes, *BRCA1* and *BRCA2*, are involved in DNA damage repair through their association with the HR mediator, RAD51, and their mutations are usually known to contribute to the tumorigenesis of hereditary breast and ovarian cancers[64]. Recent studies have further suggested that *BRCA1* mutations in females below the age of 50 years increase the risk of colorectal cancer[65], and *BRCA2* mutations are closely associated with pancreatic carcinogenesis[66,67]. RING finger protein 43, which is an E3-type ubiquitin ligase, has been reported to be mutated in pancreatic cancer[46] and gastric cancer[47] and was recently reported to act as a regulator of ATM-ATR DNA damage response; its mutation is associated with a high risk of developing sessile-serrated adenomas[48], which are believed to lead to colorectal cancer. The genes reported to have alternative splicing mutations in gastrointestinal cancers are summarized in Table 1. From the above examples, we can conclude that alternative splicing mutations in DNA damage response genes are closely associated with gastrointestinal carcinogenesis.

OTHER ALTERNATIVELY SPLICED GENES THAT RELATE TO GASTROINTESTINAL CANCERS

As mentioned above, alternative splicing is closely associated with gastrointestinal cancers and has an important role in their tumorigenesis. Gastrointestinal cancers are malignancies of the gastrointestinal tract and accessory organs of digestion, including the esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus. They account for a large proportion of human malignancies and are a major cause of morbidity and mortality worldwide[68]. Among the gastrointestinal cancers, colorectal cancer is the third most frequently diagnosed cancer worldwide after lung and breast cancers, with 1.23 million diagnosed cases (9.7% of cancer diagnoses) in 2008[69]. There are many genetic and epigenetic changes that occur during colorectal carcinogenesis, including mutations of oncogenes, tumor suppressor genes, and mismatch repair genes; genetic instability; allelic losses in specific chromosomal arms; and methylation changes in gene promoters[70]. In addition, alternative splicing mutations have an important role in gastrointestinal carcinogenesis. In particular, alternatively spliced CD44 variants promote intestinal tumorigenesis induced by the activation of Wnt signaling[41]. Osteopontin splice variant (OPN-b) is found to be dominantly elevated in gastric cancer cell lines, and OPN-b has been shown to promote gastric cancer cell survival by regulation of Bcl-2 family proteins and CD44v expressions[71]. The cyclin-dependent kinase inhibitor gene, which encodes P27, has

Table 1 List of alternatively spliced genes in gastrointestinal cancers

Genes	Role in DDR	Gastrointestinal Cancers	Reference papers
DDR-related genes in gastrointestinal cancers			
ATM	DNA damage response kinase involved in HR pathway of DNA repair	Colon cancer cells	[18]
MSH2, MLH1, MHS6, PMS2	Involved in DNA mismatch repair	Colorectal cancer and gastric cancers	[37-39,44,45,57]
MRE11	Component of DNA damage sensor complex MRN	Colorectal cancer	[36]
PARP-1	Involved in single stranded DNA damage repair Plays role in controlling HR pathway	Gastric cancer	[63]
RNF43	Function as a regulator of ATM/ATR/DNA damage response	Pancreatic cancer Gastric cancer Sessile serrated adenomas	[46] [47] [48]
AP4	Activation by cellular stresses result in DNA damage inducer of EMT	Mediates EMT in colorectal cancer lines cancer	[84,85]
BRCA1	Involved in HR	Colorectal cancer	[65]
BRCA2	Involved in HR	Pancreatic cancer	[66,67]
U2AF65	With biotinylated triplex DNA affinity	Colorectal cancer	[61]
FIR (PUF60)	Originally a transcriptional facor, also reported as a molecular sensor for bleomycin-induced DNA damage pathway	Colorectal cancer Hepatocellular carcinoma	[40,96,97] [9]
Other genes in gastrointestinal cancers			
P53	Tumor suppressor, guardian of the genome	Colon cancer, head and neck cancer	[10]
CD44	Class I transmembrane glycoprotein involved in cell adhesion, cell-cell interactions, migration and important player in stem cells and cancer	Intestinal tumorigenesis	[41]
OPN-b	Osteopontin splice variant, contributed to gastric cancer cell survival by regulation of Bcl-2 family proteins and CD44v expressions	Gastric cancer	[71]
p27 (CDKN1B)	Cell cycle regulatory gene	Small intestine neuroendocrine tumors	[72]
c-KIT	Stem cell growth factor receptor, also known as CD117	Gastrointestinal stromal tumors	[75]
Prrx1	Paired related homoeobox 1, a newly reported EMT inducer	Pancreatic cancer Colorectal cancer	[94] [95]
HDM2	Human double minute 2, negative regulator of p53	Colorectal cancer	[79]
PKM2	Pyruvate kinase M2 gene, inactive state is associated with tumor cell proliferation, could switch between PKM2 to PKM1	Impaired colorectal cancer growth	[82]
BRAF	Raf kinase family member BRAF is a proto-oncogen replays a role in regulating the MAP kinase/ERKs signaling pathway	Malignant melanomas Colorectal cancer	[77]
BMP	Bone morphogenetic proteins, are a group of growth factors, function in the formation of bone and cartilage,constitute morphogenetic signals *etc.*	Gastric cancer	[42]
PRPF6	Pre-mRNA processing factor 6, a member of the tri-snRNP spliceosome complex	Colon cancer	[34,35]
Dystrophin	Cause of Duchenne muscular dystrophy	Metastatic GIST	[76]
FGFR2	The fibroblast growth factor receptor 2, encodes for a fibroblast growth factor-activated transmembrane receptor tyrosine kinase	Pancreatic ductal adenocarcinoma Hepatic cancer metastasis	[91]
Splicing factors in other cancers			
SRSF6	Splicing facor	Lung and colon cancers	[26]
hnRNP	Splicing facor	Glioblastoma	[27,28]
SF3B1, U2AF1 ZRSR2, SRSF2	Splicing factors	Associated with numerous malignancies	[29-33]
Ik11 (Ikaros)	Alternative splicing variant of Ikaros, a member of Ikaros family genes	B-cell lympho-proliferative disorders	[24]
Helios	A member of Ikaros family genes	T-cell leukemia	[25]
PUF60 (FIR)	FIR lacks exon5 of PUF60. FIR/PUF60 interacts with SF3B1	Colon cancer, leukemia	[40,80,97]
hnRNPM	RNA-binding protein heterogeneous nuclear ribonucleoprotein M	Breast cancer metastasis	[92]

HR: Homologous recombination; DDR: DNA damage response; EMT: Epithelial-mesenchymal transition; GIST: Gastrointestinal stromal tumors.

been reported to have recurrent somatic mutations in small intestinal neuroendocrine tumors[72]. P27 was shown to be associated with proliferative activity of gastric cancer[73,74]. Approximately 85%-95% of gastrointestinal stromal tumors (GIST) have mutations in the *c-KIT* gene[75]. Dystrophin is expressed in the nonneoplastic and benign counterparts of GIST, but inactivation of dystrophin was observed in 96% of metastatic GIST. Deletion of the dystrophin-encoding and muscular dystrophy-associated DMD gene through alternative splicing led to inactivation of larger dystrophin isoforms and contributed to tumor formation and metastasis[76]. Mutations in the bone morphogenetic protein signaling pathway led to the development of juvenile polyposis syndrome, which increases the risk of gastric cancer development[42]. The Raf kinase family member, BRAF, is a proto-oncogene that has been reported to be frequently mutated in numerous human cancers, such as somatic missense mutations, in 66% of malignant melanomas and at lower frequency in colorectal cancers[77]. Murine double minute 2, which is a negative regulator of the tumor suppressor gene p53, was shown to be alternatively spliced under DNA dam-

age and contributed to numerous tumorigenesis, and its alternative splicing is mediated by FBP1 (FUBP1)[78]. The human counterpart is the negative regulator of p53, human double minute 2, which is frequently mutated by alternative splicing in colorectal cancer[79]. FUBP1 is a *c-myc* transcriptional activator[80]. Coupling of splicing and transcription should be considered and analyzed for better understanding of carcinogenesis. The pyruvate kinase muscle (*PKM*) gene is alternatively spliced to either M1 (PKM1) or M2 (PKM2) isoforms. PKM2 mostly promotes cancer cell growth, and PKM1 is usually expressed in normal differentiated tissues[81,82]. PKM2 itself is not necessary for tumor cell proliferation, and the inactive state of PKM2 has been shown to be associated with tumor cell proliferation, whereas nonproliferating tumor cells require activation of PKM[83]. MicroRNAs, such as miR-124, miR-137, and miR-340, have been shown to regulate alternative splicing of the PKM gene to switch PKM expression from PKM2 to PKM1 and contribute to impaired colorectal cancer growth[82]. Studies have suggested many alternative splicing isoforms of genes, such as *VEGFA*, *UGT1A*, *PXR*, cyclin D1, *BIRC5* (survivin), *DPD*, *K-RAS*, *SOX9*, and *SLC39A14*, are potential therapeutic targets of colorectal cancers[43]. In brief, alternative splicing variants are potential targets for both diagnosis and treatment of gastrointestinal cancers.

ALTERNATIVE SPLICING IS CLOSELY ASSOCIATED WITH CANCER METASTASIS

Alternative splicing variants of certain genes not only have important roles in tumorigenesis but also significantly contribute to cancer metastasis. For example, the transcription factor, AP4, is encoded by the p53 tumor-suppressor gene and activated by numerous cellular stresses, which generally result in DNA damage[84]. AP4 is an inducer of epithelial-mesenchymal transition (EMT) and mediates c-MYC-induced EMT in colorectal cancer cell lines[85]. EMT of tumor cells contributes to metastasis[86,87]. Mesenchymal-epithelial transition (MET), which presumably contributes to tumor suppression[88], has been shown to be induced by p53 activation. Most recently, Peng *et al*[89] summarized the role of EMT in gastric cancer and suggested that loss of E-cadherin *via* its transcriptional repressors, such as Snail, ZEB, and Twist, is a key step in EMT activation, which significantly contributes to gastric carcinogenesis. Fibroblast growth factor receptor 2 (FGFR2) encodes for a fibroblast growth factor-activated transmembrane receptor tyrosine kinase and has been shown to be associated with EMT-related alternative splicing[90]; its alternative splicing generates the ⅢⅠb and ⅢⅠc isoforms. FGFR-2 ⅢⅠb expression correlates with venous invasion of pancreatic ductal adenocarcinoma, whereas FGFR-2 ⅢⅠc expression correlates with faster development of liver metastasis[91]. RNA-binding protein heterogeneous nuclear ribonucleoprotein M promotes breast cancer metastasis by activating the switch of alternative splicing that occurs during EMT[92]. Recently, splicing of paired related homoeobox 1 (Prrx1) has been reported to be a novel EMT-MET switch. Alternative splicing of Prrx1 results in two variants, Prrx1a and Prrx1b, and the ratio of Prrx1a (with inhibition domain)/Prrx1b (lack of inhibition domain)[93] switches EMT-MET of cells and controls migration and invasion of pancreatic cancer[94]. Notably, Prrx1 is involved in metastasis and poor prognosis in colorectal cancer[95].

CLINICAL APPLICATION OF ALTERNATIVE SPLICING TO CANCER DIAGNOSIS AND TREATMENT

Alternative splicing variants can be potential targets for the diagnosis and treatment of many cancers, including gastrointestinal cancers (Figure 2)[43,96]. Novel splicing variants of FIR were generated by SAP155 siRNA, and these variants were also found to be activated in human colorectal cancer tissues[97]. Circulating FIR and FIRΔexon2 mRNAs are potential novel screening markers for colorectal cancer testing with conventional carcino-embryonic antigen and carbohydrate antigen 19-9. Given the central role of c-Myc in the development of many cancers, one direction toward the development of cancer gene therapies directed against c-Myc may go through FIR and its variants. The *Sendai virus* vector of FIR has shown strong tumor growth suppression with no significant side effects in an animal xenograft model and is potentially applicable to future clinical cancer treatment[98].

CONCLUSION

Alternative splicing is a fundamental process of gene regulation in eukaryotes. It is a common phenomenon in mammalian genomes because most human genes undergo this process[4]. Alternative splicing leads to genetic instability, such as CIN, which drives tumorigenesis. DNA damage is one of the major reasons for genetic instabilities, and major components of the DNA damage repair pathway are alternatively spliced in certain cancers. Therefore, alternative splicing is closely associated with tumorigenesis by contributing to genetic instability. Alternative splicing of DNA damage repair proteins is a significant cause of gene mutations, which reciprocally affects alternative splicing in cancer. DNA damage promotes genetic instability, and genetic instability further promotes tumorigenesis (Figure 1). Genetic instability caused by certain types of DNA damage may be critical for the development of all colorectal cancers[55]. Many genes involved in the DNA damage repair pathway are alternatively spliced in gastrointestinal cancers (Table 1). Thus, the alternative splicing in DNA damage response-related genes has an important role in the tumorigenesis, survival, and growth of gastrointestinal cancers. Establishing a well-organized database of alternative splicing

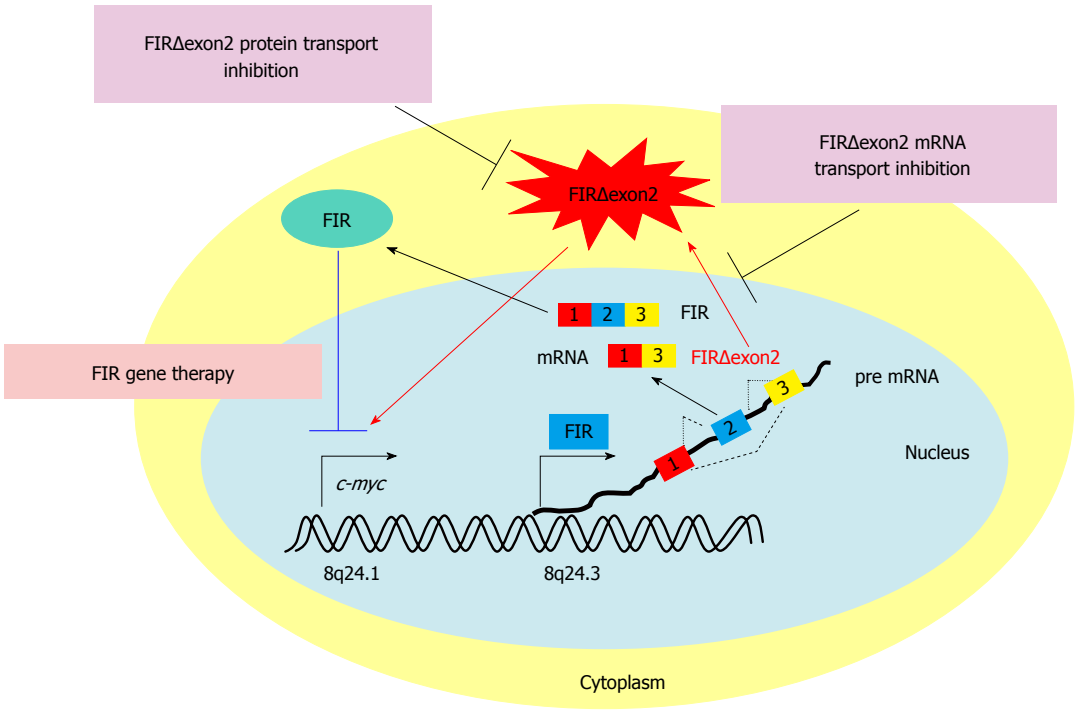

Figure 2 A model of cancer diagnosis and treatment targeting alternatively spliced variant forms. c-Myc has a critical role in cell proliferation and tumorigenesis. An far upstream element binding protein-interacting repressor (FIR) splice variant that lacks exon 2 (FIRΔexon2) activates *c-myc* transcription by disabling authentic FIR repression of *c-myc* in cancer cells[40]. FIR gene therapy is a potential cancer treatment[98]. FIRΔexon2 protein inhibition of transport into the nucleus and/or FIRΔexon2 mRNA inhibition of export into the cytoplasm may be potential molecular targets for future cancer therapy for suppression of c-Myc. FIR and/or FIRΔexon2 mRNAs in peripheral blood are potent biomarkers for cancer detection[97].

would be helpful for facilitation of the process of considering a set of splice isoforms or their common regulatory network as targets of diagnostic or therapeutic strategies. Better understanding of the role and mechanism of alternative splicing in tumorigenesis may lead to novel directions for future cancer studies.

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