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Selected Publications:

A. Mayeda, K. Tatei, H. Kitayama, K. Takemura, Y. Ohshima (1986). Three distinct activities possibly involved in mRNA splicing are found in a nuclear fraction lacking U1 and U2 RNA. *Nucleic Acids Res.* **14,** 3045–3057.

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K. Ohe, **A. Mayeda** (2010). HMGA1a trapping of U1 snRNP at an authentic 5' splice site induces aberrant exon skipping in sporadic Alzheimer's disease. *Mol. Cell. Biol.* **30,** 2220–2228.

N. Sasaki-Haraguchi, M.K. Shimada, I. Taniguchi, M. Ohno, **A. Mayeda** (2012). Mechanistic insights into human pre-mRNA splicing of human ultra-short introns: Potential unusual mechanism identifies G-rich introns. *Biochem. Biophys. Res. Commun.* **423,** 289–294.

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M.A. Rahman, A. Masuda, K. Ohe, M. Ito, D.O. Hutchinson, **A. Mayeda**, A.G. Engel, K. Ohno (2013). HnRNP L and hnRNP LL antagonistically modulate PTB-mediated splicing suppression of *CHRNA1* pre-mRNA. *Sci. Rep.* **3,** 2931.

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K. Fukumura, S. Wakabayashi, N. Kataoka, H. Sakamoto, Y. Suzuki, K. Nakai, **A. Mayeda** & K. Inoue (2016). The exon junction complex controls the efficient and faithful splicing of a subset of transcripts involved in mitotic cell-cycle progression. *Int. J. Mol. Sci.* **17**, 1153.

Considerable Implications of Unexpectedly Prevalent Multi-Step Splicing

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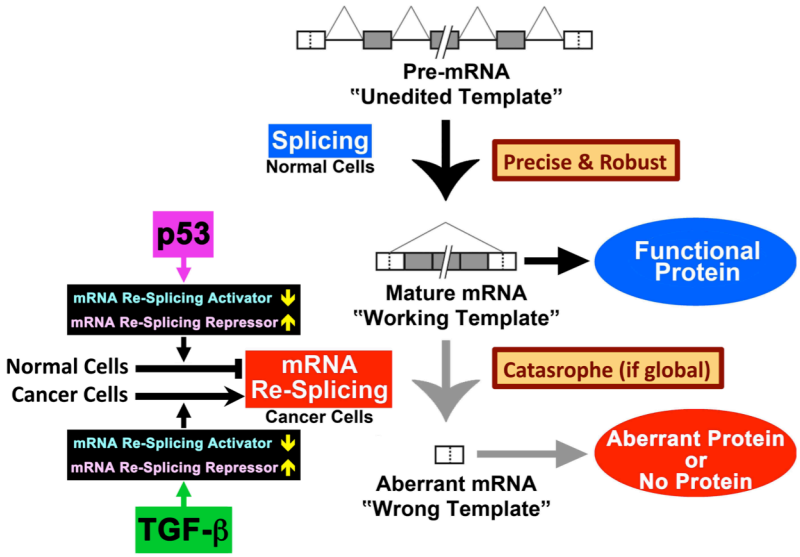
Multi-step sequential pre-mRNA splicing events, such as 'recursive splicing' and 'nested splicing', to remove very large introns are unexpectedly prevalent in human [*EMBO J.* **27**, 122 (2008); *FEBS Letters.* **587**, 555 (2013); *Nucleic Acids Res.* **43**, 4721 (2015); *Nature*. **521**, 371 (2015); *RNA Biol.* **13**, 290 (2016)]. In contrast to these multi-step splicing events in normal cells, we discovered mRNA re-splicing in cancer cells that occurs on mature spliced mRNA and generates aberrant transcripts/proteins [*Nucleic Acids Res.* **40**, 7896 (2012)]. The mRNA re-splicing in various cancer cells implies an important mechanism that prevents deleterious extra re-splicing in normal cells, while the re-splicing could be promoted by unknown factor(s) overexpressed or repressed in cancer cells (see Figure).



Recent striking three findings from our group and Taiwanese group represent a breakthrough in the study of mRNA re-splicing. **(1) The function of cancer-specific spliced product of *TSG101* gene was discovered.** The human TSG101Δ154–1054 (TSG101Δ) mRNA was a major aberrantly spliced product detected in various cancer cells/tissues, and we first demonstrated the exact pathway of this aberrant splicing, that was re-splicing of normally spliced TSG101 mRNA [*Nucleic Acids Res.* **40**, 7896 (2012)]. TSG101Δ protein product increases TSG101 stability by competitively inhibiting its E3 ligase-mediated proteasomal degradation [*Oncotarget* **7**, 8240 (2016)]. Therefore, TSG101Δ, i.e., re-splicing of TSG101, specifically enhances TSG101-stimulated cell proliferation and tumor growth. **(2) mRNA re-splicing is stimulated by epithelial-mesenchymal transition factor TGF-β.** We found mRNA re-splicing is significantly promoted by the expression of TGF-β (see Figure). TGF-β is closely involved in cancer metastasis and invasion, which might be implicated in mRNA re-splicing event. **(3) mRNA re-splicing is repressed by the expression of tumor suppressor gene p53 (*TP53*).** Cultured cells expressing wild-type p53 fully inhibits TSG101Δ production and knock-down of p53 restores TSG101Δ generation (see Figure) [*Oncotarget* **7**, 8240 (2016)]. This result indicates that the regulation of mRNA re-splicing is under the control of p53. Therefore, our goal, to identify mRNA re-splicing regulatory factors (either activator or repressor), can be searched within the subset of factors that are controlled by the p53 expression (see Figure).