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Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders & Cancer

Positions

Professor, Sackler Faculty of Medicine

Research

By utilizing the unique strengths of our research group in bioinformatic analyses as well as in genomic and advanced molecular biology methodologies, we are able to make groundbreaking discoveries in the field of alternative splicing. We study how alternative splicing generates higher level of organism complexity, especially in human. However, this comes with a price, and alternative splicing also inflicts many genetic disorders and cancer. Our research involves these two facets of alternative splicing. On one hand, we found how new functions evolved via the generation of new exons (mostly in human). We have also showed how different layers of gene expression affect each other, and found that chromatin organization and epigenetic markers (DNA methylation) mark the exon-intron structure. We also found that during the evolution of warm-blooded organisms two exon-intron gene architectures developed, and these also reflect the different effects of mutations on splicing in cancer and other genetic disorders. On the other hand, we study the impact of splicing abnormalities on colon and lung cancer, and we have recently discovered a new therapy for Familial Dysautonomia, a neurodegenerative disease caused by a splicing defect in the nervous system.

Publications

Fuchs G, Hollander D, Voichek Y, Ast G, Oren M. (2014) Cotranscriptional histone H2B monoubiquitylation is tightly coupled with RNA polymerase II elongation rate. *Genome Res*. 24:1572-83.

Gelfman S, **Ast G**. When epigenetics meets alternative splicing. (2013) The roles of DNA methylation and GC architecture. *Epigenomics*. 2013:351-353.

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Bochner R, Ziv Y, Zeevi D, Donyo M, Abraham L, Ashery-Padan R, **Ast G**. Phosphatidylserine increases IKBKAP levels in a humanized knock-in IKBKAP mouse model. (2013) *Hum Molec Genet*. 22: 2785-2794

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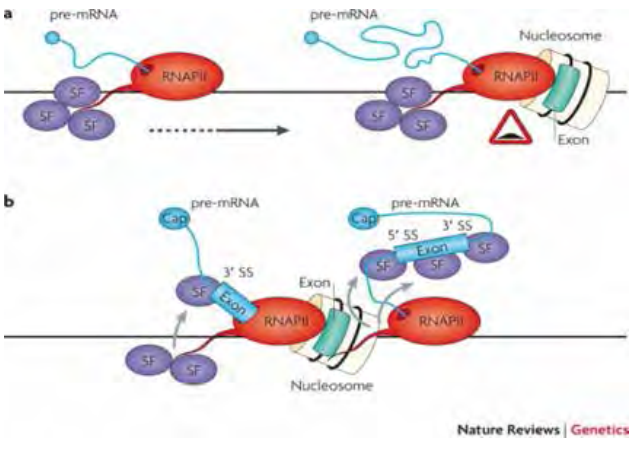

Nucleosome occupancy marks exons and is coupled to transcription. **a.** RNA polymerase II (RNAPII), associated with different splicing factors (SFs), travels along the gene and transcribes it. When RNAPII reaches an area with high nucleosome occupancy and encounters specific histone modifications that mark an exon, it is slowed down. **b.** This panel shows RNAPII and the nucleosome at the point at which their coupling marks the exon boundaries for the splicing machinery. RNAPII transcribes the exon and SFs detach from the carboxy-terminal domain of RNAPII and bind to the 3′ splice site (3′ SS) region of the precursor mRNA (pre-mRNA). During transcription elongation, additional SFs bind intronic and exonic splicing regulatory elements and the 5′ SS.

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Cheishvili D, Maayan C, Cohen-Kupiec R, Lefler S, Weil M, **Ast G**, Razin A. (2011) IKAP/Elp1 involvement in cytoskeleton regulation and implication for familial dysautonomia. *Hum Mol Genet*. 20:1585-1594.

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Reviews

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Schraga Schwartz and **Ast G**. (2010) Chromatin density and splicing destiny: on the cross-talk between chromatin structure and splicing. *EMBO J*. 29:1629–1636.

Keren H, Lev-Maor G, **Ast G**. (2010) Alternative splicing and evolution: diversification, exon definition and function. *Nature Rev Genet.* 11:345-355.

Grants

2012-2015 ISF- Morasha for Neurodegenerative Diseases, Tissue-specific alternative splicing disease

2013-2015 Teva – Neuroscience, Evaluation of therapeutic agents in a mouse model for Familial Dysotonomia

2013-2018 Israel Science Foundation, Identification of novel determinants of splicing regulation

2014-2015 Israel Cancer Research Fund (ICRF) Project Grant