Jan-Growth Chang, Asian J Biomed Pharmaceut Sci, Volume:9
DOI: 10.4066/2249-622X-C2-019

allied academies

9th World Congress on
Chemistry and Medicinal Chemistry
May 13-14, 2019 | Prague, Czech Republic

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Modulating of RNA Alternative Splicing for the treatment of Cancer and Genetic Diseases

RNA alternative splicing (AS) is a regulatory mechanism of gene expression that allows cells to generate more than one mRNA species from a single gene. AS can produce mRNAs which differ in their untranslated regions or coding area through exon skipping, mutually exclusive exons, the use of AS sites, and introns retention. There difference may influence mRNA stability, localization, or translation. AS may contribute to cell differentiation and lineage determination, tissue-identity acquisition and maintenance, and organ development. AS is highly regulated, disturbance of AS machinery leads to mis-splicing, and may result in a range of diseases including cancer, genetic diseases and neurodegenerative disorders. Understanding of the mechanism of AS result in the disease is very important for designing effective therapeutic strategies.

The spatiotemporal changes of AS are governed by combination of cis-regulatory elements and cognate trans-acting factors, which promote or inhibit spliceosome assembly. AS is also controlled by coordinated interactions with other regulatory layers, including transcription and chromatin. Moreover, post-translational and signaling pathways influence AS through different mechanisms, such as by altering the function and/or localization of key splicing regulators. This extensive crosstalk between gene regulatory layers including dynamic spatial, physical and temporal organizational properties of the cell nucleus, and further emphasizes the importance of developing a multidimensional understanding of AS, and also provides a theoretical basis of drug design for the treatment of AS-relate diseases and cancer.

To interrogate the treatment of AS-related diseases and cancer, we have developed cell line-system to screen AS-modulating small molecules and using animal model to test their therapeutic effects. More than 500 compounds have been screened, and we found several small molecules have been found to affect the AS of the causing gene of SMA, Fibry's disease, and cancer including modulation of drug resistance. From our results, we suggest that AS-related drugs may affect different layers of AS regulatory machinery, and this effect may influence the therapeutic effect on the diseases. In this talk, I am going to share our previous experience, and present our recent research.

Speaker Biography

Jan-Growth Chang is an expert in the field of molecular diagnosis and treatment of genetic disease and cancer. He was one of the pioneers of the spinal muscular atrophy treatment using small molecules. He was the pioneer to study the diuretic drug-amiloride and its derivatives on RNA alternative splicing and explored their roles at the treatment of cancer and genetic diseases. He has also developed many methods to detect the genetic lesions of genetic diseases and cancer. He is author of over 350 papers and owner of several patents. Now, he is Vice-Superintendent of China Medicine University Hospital, and Director of Department of Laboratory Medicine, Center for Precision Medicine, and Epigenome Research center.

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