RNA epitranscriptomics

RNA epitranscriptomics is a field of molecular biology that focuses on the study of chemical modifications to RNA molecules, known as RNA modifications or epitranscriptomic modifications. These modifications occur after RNA is transcribed from DNA and can influence various aspects of RNA function, including stability, translation, and interactions with other molecules. RNA epitranscriptomics has gained significant attention in recent years as researchers have discovered that these modifications play crucial roles in regulating gene expression and various cellular processes.

Here are some key aspects of RNA epitranscriptomics:

RNA Modifications: RNA molecules can undergo various chemical modifications, including but not limited to methylation (addition of methyl groups), acetylation (addition of acetyl groups), pseudouridylation (conversion of uridine to pseudouridine), and more. These modifications occur on the nucleotide bases or the ribose sugar of RNA.

Enzymatic Writers and Erasers: RNA modifications are installed by specific enzymes called “writers” and removed by enzymes known as “erasers.” The balance between these enzymes can determine the overall modification status of an RNA molecule.

Reader Proteins: Proteins known as “reader” proteins can recognize and bind to specific RNA modifications. These reader proteins can then affect various RNA functions, such as RNA processing, localization, translation, and stability.

Biological Functions: RNA modifications are involved in various biological processes, including gene regulation, cellular differentiation, response to stress, and immune responses. They can influence the secondary structure of RNA and its interactions with other RNA molecules, proteins, or small molecules.

RNA Splicing: RNA modifications can impact alternative splicing events, leading to the generation of different RNA isoforms and protein variants from a single gene.

Translation Regulation: Some RNA modifications can affect the efficiency of translation, influencing the production of specific proteins. This regulation can be important in cellular responses to changing environmental conditions.

Disease Relevance: Dysregulation of RNA modifications has been implicated in various diseases, including cancer, neurodegenerative disorders, and metabolic diseases. Researchers are exploring RNA modifications as potential diagnostic markers and therapeutic targets.

Techniques and Tools: To study RNA epitranscriptomics, researchers use a range of techniques, including high-throughput sequencing methods (such as MeRIP-Seq and m6A-Seq) and mass spectrometry to detect and quantify RNA modifications.

Emerging Research: RNA modifications, particularly N6-methyladenosine (m6A) and 5-methylcytosine (m5C), have been extensively studied in recent years. Researchers continue to discover new RNA modifications and their roles in cellular processes.

RNA epitranscriptomics is a rapidly evolving field that has the potential to deepen our understanding of gene regulation and cellular responses to various stimuli. It is also a promising area for the

development of new therapeutic strategies and diagnostic tools in the future.

The study of transcriptomics, also referred to as expression profiling, examines the expression level of mRNAs in a given cell population, often using high-throughput techniques based on DNA microarray technology. The use of next-generation sequencing technology to study the transcriptome at the nucleotide level is known as RNA-Seq.

Although gene co-expression networks typically do not provide information about causality, emerging methods for differential coexpression analysis are enabling the identification of regulatory genes underlying various phenotypes.

The application of deep learning methods to transcriptomic data has the potential to enhance the accuracy and efficiency of tissue classification and cell state identification. Herein, we developed a multitask deep learning model for tissue classification combining publicly available whole transcriptomic (RNA-seq) datasets of non-neoplastic, neoplastic, and peri-neoplastic tissue to classify disease states, tissue origin, and neoplastic subclass. RNA-seq data from a total of 10,116 patient samples processed through a common pipeline were used for model training and validation. The model achieved 99% accuracy for disease state classification (ROC-AUC of 0.98) and 97% accuracy for tissue origin (ROC-AUC of 0.99). Moreover, the model achieved an accuracy of 92% (ROC-AUC 0.95) for neoplastic subclassification. This is the first multitask deep learning algorithm developed for tissue classification employing a uniform pipeline analysis of transcriptomic data with multiple tissue classifiers. This model serves as a framework for incorporating large transcriptomic datasets across conditions to facilitate clinical diagnosis and cell-based treatment strategies [1)]

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van Dam et al. introduced and guide researchers through a (differential) co-expression analysis. They provide an overview of methods and tools used to create and analyse co-expression networks constructed from gene expression data, and they explain how these can be used to identify genes with a regulatory role in disease. Furthermore, they discuss the integration of other data types with co-expression networks and offer future perspectives of co-expression analysis [2)].

Specific chemical modifications of biological molecules are an efficient way of regulating molecular function, and a plethora of downstream signalling pathways are influenced by the modification of DNA and proteins. Many of the enzymes responsible for regulating protein and DNA modifications are targets of current cancer therapies. RNA epitranscriptomics, the study of RNA modifications, is the new frontier of this arena. Despite being known since the 1970s, eukaryotic RNA modifications were mostly identified on transfer RNA and ribosomal RNA until the last decade, when they have been identified and characterized on mRNA and various non-coding RNAs. Increasing evidence suggests that RNA modification pathways are also misregulated in human cancers and may be ideal targets of cancer therapy. In this Review we highlight the RNA epitranscriptomic pathways implicated in cancer, describing their biological functions and their connections to the disease [3)].

RNA modifications play a major role in tumorigenicity and progression, but the expression and function in glioblastoma (Glioblastoma) have not been well described. In a study, Li et al. developed a Glioblastoma score based on the differentially expressed genes (DEGs) between groups showing RNA modification patterns. They assessed the association between the Glioblastoma score and tumor microenvironment (TME) characteristics. Based on the gene expression of these regulators, they identified two clusters with distinct RNA modification patterns. Kaplan-Meier survival curves showed that patients in cluster 1 had worse survival than those in cluster 2. Kaplan-Meier and multivariate Cox regression analyses showed that Glioblastoma scores (based on DEGs between RNA modification patterns) are an independent predictive biomarker for patient prognosis. Besides, they found that samples with high scores were significantly associated with epithelial-to-mesenchymal transition and immune checkpoints, while samples with low scores were associated with cell cycle regulation. Importantly, Glioblastoma-score markedly positively correlated with drug resistance, while negatively correlated with drug sensitivity. The responders of anti-PD-1/PD-L1 immunotherapy tend to have a lower Glioblastoma score than non-responders. In conclusion, a comprehensive analysis of multiple RNA modifications in Glioblastoma revealed that RNA modification regulators were closely correlated with tumor microenvironment (TME) [4].

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Hong J, Hachem LD, Fehlings MG. A deep learning model to classify neoplastic state and tissue origin from transcriptomic data. Sci Rep. 2022 Jun 11;12(1):9669. doi: 10.1038/s41598-022-13665-5. PMID: 35690622.
2)
van Dam S, Võsa U, van der Graaf A, Franke L, de Magalhães JP. Gene co-expression analysis for functional classification and gene-disease predictions. Brief Bioinform. 2018 Jul 20;19(4):575-592. doi: 10.1093/bib/bbw139. PubMed PMID: 28077403; PubMed Central PMCID: PMC6054162.
3)
Barbieri I, Kouzarides T. Role of RNA modifications in cancer. Nat Rev Cancer. 2020 Jun;20(6):303-322. doi: 10.1038/s41568-020-0253-2. Epub 2020 Apr 16. PMID: 32300195.
4)
Li G, Zhu Y, Gu J, Zhang T, Wang F, Huang K, Gu C, Xu K, Zhan R, Shen J. RNA modification patterns based on major RNA modifications define tumor microenvironment characteristics in glioblastoma. Sci Rep. 2022 Jun 18;12(1):10278. doi: 10.1038/s41598-022-14539-6. PMID: 35717510.