eJBio

Electronic Journal of Biology, 2023, Vol. 19(1):1-2

An Outline of Plans and Progress Post-Transcriptional Modification

Clarke Kitney*

Departments of Entomology and Ecology & Evolutionary Biology, Cornell University, USA

***Corresponding author:** Email: kitney_c@gmail.com

Citation: Kitney C (2023) An Outline of Plans and Progress Post-Transcriptional Modification. Electronic J Biol, 19(1): 1-2

Received date: December 11, 2022, Manuscript No. IPEJBIO-23-15928; **Editor assigned date:** December 13, 2022, PreQC No. IPEJBIO-23-15928 (PQ); **Reviewed date:** December 24, 2022, QC No. IPEJBIO-23-15928; **Revised date:** January 04, 2023, Manuscript No. IPEJBIO-23-15928 (R); **Published date:** January 11, 2023, DOI: 10.36648/1860-3122.19.1.061

Description

Targeted therapies and immune checkpoint inhibitors have advanced the treatment landscape of Renal Cell Carcinoma (RCC) over the last decade. While checkpoint inhibitors have demonstrated survival benefit and are currently approved in the front-line and second-line settings, primary and secondary resistance is common. A comprehensive understanding of the mechanisms of immune evasion in RCC is therefore critical to the development of effective combination treatment strategies. This article reviews the current understanding of the different, yet coordinated, mechanisms adopted by RCC cells to evade immune killing; summarizes various aspects of clinical translation thus far, including the currently registered RCC clinical trials exploring agents in combination with checkpoint inhibitors; and provides perspectives on the current landscape and future directions for the field.

There are a variety of mechanisms by which RCC evades the immune system. They can be categorizing into 7 subsections: (i) immune checkpoint signaling; (ii) loss of antigen-presenting ability; (iii) tumor-associated gangliosides; (iv) tumor-associated metabolites; (v) tumor-promoting immune cells in the microenvironment and their inhibitory cytokines; (vi) other mechanisms inhibiting effector CD8+T cells and Natural Killer (NK) cells; and (vii) impaired immune cell trafficking.

The rate and speed with which cancer biology discoveries translate into clinical practice have importance for oncologists, researchers, and policy makers. A prior study found that among 101 science articles claiming a highly promising result for clinical translation, only 19 of 101 (18.8%) interventions had positive randomized trials, whereas five had been licensed for clinical use with a median follow-up of 12 years.

This analysis, however, spanned all disciplines, and, to our knowledge, no study has investigated how frequently 'highly promising' cancer discoveries lead to actionable clinical treatments in cancer medicine.

Highly Promising Discoveries

On 23 July 2019, we searched PubMed for articles published between 1999 and 2009 that include the search term 'cancer' in the title or abstract along with 'highly promising', 'groundbreaking', 'landmark', or 'breakthrough'. We included all original publications describing therapies or preventive treatments while excluding early detection and nontherapeutic studies. We only considered studies that remained in the experimental stage including in vitro and in vivo cellular models, animal models, or nonrandomized human trials. We also considered reviews and commentaries of experimental phase research. Randomized controlled trials and meta-analyses were excluded.

For each 'highly promising' strategy, we performed a mixed methods search to identify clinical success by the date of 3 June 2020. First, we compared the target and/or compounds against all FDA-approved therapies in cancer medicine. Second, we discussed with a practicing hematologist–oncologist (VP) to see if the doctor had exposure to products related to the claim. Third, we performed Google searches, using keywords, including, but not limited to, drug, target, strategy, method, reagent, company, and/or chemical name. This allowed us to build a set of adopted therapies.

For each FDA-approved drug, we determined the clinical endpoint utilized for approval. Of these treatments, 12/17 (70.6%) had a surrogate endpoint as the primary outcome measure, with 8/17 (47.1%) demonstrating an overall survival benefit or 8/88 (9.1%) overall. These claims represent 12 distinct approvals (therapy/indication combinations) of which 9/12 (75%) were approved based on surrogate endpoints as the primary outcomes with six based on progression-free survival and one each based on durable response rate, duration of locoregional control, or the development of precancerous changes. Of these 12 distinct approvals, 5 (41.7%) had demonstrated overall survival benefits, with a mean of 6.0 months and a median of 2.8 months.

YTHDF1 is the most versatile and powerful reader protein of N6-methyladenosine (m6A)-modified RNA, and it can recognize both G(m6A)C and A(m6A)C RNAs as ligands

without sequence selectivity. YTHDF1 regulates target gene expression by different mechanisms, such as promoting translation or regulating the stability of mRNA. Numerous studies have shown that YTHDF1 plays an important role in tumor biology and nontumor lesions by mediating the protein translation of important genes or by affecting the expression of key factors involved in many important cell signaling pathways. Therefore, in this review we focus on some of the roles of YTHDF1 in tumor biology and diseases.

Post-Transcriptional Modification

Post-transcriptional modification of RNA, which includes capping, splicing, and polyadenylation, is regarded as a key factor controlling mammalian protein production. The N6-methyladenosine (m6A) modification, which is the most abundant conserved post-translational modification, is found in a wide range of cellular RNAs. In recent years, m6A modifications have been shown to have an important function in the progression of various metabolic, infectious, immune system, and cardiovascular diseases and cancers. The RNA base sequence DRACH (D=A/G/U, R=A/G, H=A/C/U) is the consensus site of m6A.

m6A modification on RNA polymerase II (pol II) transcribed RNAs such as mRNAs, long noncoding RNAs (lncRNAs), precursors of microRNAs, or circular RNAs can mediate their gene expression.

m6A is regulated by an evolutionarily conserved methylase complex known as the “writers” complex including ZC3H13, RBM15, KIAA1429, METTL3, METTL14, and WTAP. It can also be reverted to an unmodified form by a demethylase family of “erasers,” including FTO and ALKBH5.

The pocket of the YTH domain governs m6A-specific recognition. The m6A binding pocket of the YTHDF1 YTH domain is composed of the N terminus of α2, the C termini of β1, α1, and β2, and the loop between β4 and β5. Specifically, m6A is accommodated in a pocket, which is made up of Trp411, Trp465, and Trp470, with the ring planes of Trp411 and Trp470 parallel to each other and perpendicular to the ring plane of Trp465. The N6-methyl moiety and the aromatic cage form CH-π interactions; similarly, the adenine base and the aromatic residues form π-π interactions. As a result, both interactions constitute the basis of m6A-specific recognition.