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Drug Development for Cancer Treatment

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Abstract

To provide the RNA and protein complexity needed to control gene expression, RNA editing is essential. Correct RNA editing preserves organism development and cell function. Diseases and cancer may result from an imbalance in the RNA editing machinery. Though few studies have been reported in the realm of natural products that target RNA editing for disease and cancer therapy, it has recently been acknowledged as a target for drug discovery. Therefore, medicinal natural compounds may be able to target RNA editing. We present a literature summary of the biological effects of RNA editing on gene expression, illnesses, malignancies, and medications in this study. Additionally, a summary of the RNA editing bioinformatics resources was provided.

Keywords: Drug discovery; Drug Development; Cancer therapy; RNA editing; Bioinformatics

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Introduction

RNA editing is the modification of an RNA transcript's nucleotide sequence in relation to the encoding DNA. RNA editing can increase the diversity of RNA and proteins. Although there are five different forms of RNA editing, higher eukaryotes most frequently use adenosine-to-inosine (A-to-I) editing. The complexity of gene expression may increase as a result of the A-to-I editing due to changes in amino acid type and alternative splicing. Adenosine deaminase family proteins working on RNA are involved in the enzymatic A-to-I editing process (ADAR). Site-selective and hyper-editing, two kinds of A-to-I RNA editing, have been described. While the site-selective method often converses one or a few A-to-I sites, the hyper editing method results in the adenine deamination of lengthy sections of double-strand RNA. As a result, the transcriptome diversity benefits from a worldwide posttranscriptional alteration caused by the A-to-I RNA editing. Commonly occurring A-to-I RNA editing can change the amino acids in translated exons, affect how RNA folds, or edit non-coding exons or introns. To increase the complexity of gene expression, additional gene products and functions are produced in addition to those expressed in the original genes [1].

Many organisms depend on RNA editing. Correct RNA editing is crucial to the development of an organism. For instance, RNA editing deficiencies may manifest as harmful phenotypes in both plants and mammals. For instance, RNA editing mutants have been linked to severe abnormalities in organelle formation and male sterility due to pollen abortion. In motor neurons of amyotrophic lateral sclerosis, a glutamate receptor subunit GluR2 RNA editing deficit has been observed. As will be discussed later, illnesses and malignancies may occur as a result of RNA editing deficiencies or improper regulation.

Asymmetry in RNA editing may cause various proteins involved in typical physiology, such as brain and immunological functions, to malfunction since RNA editing is crucial for controlling gene expression in animals. Ion channels and neurotransmitter receptors are just two examples of the numerous nervous system targets that are subjected to A-to-I RNA editing by ADARs. For instance, in an animal model of depression, the RNA editing of the serotonin (5-hydroxytryptamine (5-HT)) 2C receptor (HTR2CR) was changed, and antidepressants frequently decreased its RNA editing effectiveness. Additionally, both coding and noncoding transcriptome in nervous system tissues may be subject to ADAR-mediated RNA editing. Non-coding sections like microRNA and the 3′ translated region (UTR) of mRNAs are edited more frequently than coding areas, especially in the nervous system [2].

By modifying the RNA transcripts of immune-related genes, ADARs can control the innate immune response. ADAR (ADAR1) may have a role in controlling hepatitis delta virus RNA editing and replication (HDV). For instance, ADAR1-S and ADAR1-L both play a role in HDV editing; ADAR1-S is active in unstimulated cells while ADAR1-L is active in cells that have been stimulated by IFN-alpha. The host ADAR1 and HDV RNA structural motifs interact

during RNA editing, and these interactions may be crucial to the HDV replication cycle.

Indicating that A-to-I RNA editing is important in human embryogenesis and that disrupting the control of differentiation and apoptosis may increase cancer, it was discovered that the regulation of ADAR depends on the differentiation status of pluripotent human embryonic stem cells. Oncogene or tumour suppressor gene expression can be altered through RNA regulation. A-to-I editing is involved in cell development and is responsible for the RNA molecule's base pairing characteristics and structure alteration. As a result, A-to-I RNA editing may aid in the emergence and development of cancer [3].

For instance, when HeLa-cell-derived tumour growth rates in xenograft models were suppressed, ADAR1 was down-regulated. In mice, deletion of the ADAR1 gene causes established chronic myelogenous leukaemia to regress. Reduced A-to-I editing may play a role in the development of brain cancer, as shown by the finding that ADARB2 (ADAR3) mRNA was lowered in glioblastoma multiform. However, paediatric astrocytomas and glioblastomas were unable to proliferate due to ADARB1 (ADAR2) down regulation. Additionally, it's possible that RNA editing wasn't involved in the development of urinary bladder cancer. RNA editing targets for cancer have recently been identified, including antizyme inhibitor 1 (AZIN1) and glioma-associated oncogene 1. (GLI1). Hepatocellular carcinoma is associated with an increase in AZIN1's A-to-I RNA editing. In basal cell carcinoma tumours, there is less GLI1 transcription factor RNA editing, which is implicated in Hedgehog signalling [4].

RNA editing and other types of mRNA transcript diversity have a significant impact on drug discovery. Isoforms produced by RNA editing may offer new therapeutic targets in addition to primary gene products that have favourable physiological effects. Transcript variety consequently opens up potential new avenues for medication research, design, and therapy. It has been proposed that the treatment target for CNS illnesses is RNA editing. For instance, RNA editing of the 5HT2C receptor may have an impact on brain function, medication responsiveness, and cell signalling. Some channels, like the Kv1.1 channel, can have their drug response altered by A-to-I RNA editing. As a result, these receptors and channels may undergo RNA editing to alter their protein activities and serve as a target for disease therapy. Recently, some medications for RNA editing enzyme inhibition were found. Novel inhibitors of Trypanosoma brucei RNA editing ligase 1, for instance, have been touted as possible therapeutic agents.

Such studies are still uncommon, despite the great likelihood of discovering natural compounds that might target the RNA editing enzymes or result in the RNA editing of some target genes. Some natural items may have the capacity to block or modulate RNA editing, which could have an effect on disease and cancer treatment. As a result, we gathered RNA editing bioinformatics resources to aid researchers studying natural products in their quest to understand how they affect RNA editing [5].

Materials and Method

All participants gave their informed consent before participating in this study at Kaohsiung Medical University Hospital, which was authorised by the hospital's institutional review board (KMUHIRB-20130022). As of April 2019, 65 patients with histologically confirmed locally advanced T4 or metastatic GC were participating in the trial, which began in January 2010. Diagnostic laparoscopy will be performed in the current study when image studies cannot confirm whether the curative-intent resection could be performed in locally advanced T4 GC patients without distant metastasis. However, diagnostic laparoscopy is not routinely performed in metastatic GC patients with dissemination. Blood tests, gastroscopy with tumour biopsy samples, a thorough history review and physical examination, image studies (such as chest radiography, abdominal computed tomography (CT), and additional magnetic resonance imaging (MRI) if the CT scan was unable to determine the stage of the cancer), and other tests make up the baseline investigations. The American Joint Commission on Cancer/Union for International Cancer Control standards were used to determine TNM classification [6].

Patients with locally advanced T4 or metastatic GC that has been histologically verified are eligible for this trial. Patients should have an Eastern Cooperative Oncology Group performance status of 0–2 and be at least 18 years old. Patients must have healthy liver, kidney, and haematological functions. The following are exclusion criteria: life expectancy 3 months, prior radiotherapy or chemotherapy, inability to receive neoadjuvant therapy, metastases in the central nervous system or prior malignancy, active infections, or serious concurrent medical illnesses (such as clinically significant cardiac disease or liver disease, known peripheral neuropathy). Neoadjuvant chemotherapy, radiation, or another treatment option was selected following patient and family discussions and consideration of the patient's qualifying requirements, taking into account Taiwanese real-world conditions [7].

In this research, we included patients who had metastases to the liver, lungs, or bones. Patients with GC who had liver, lung, and bone metastases along with neoadjuvant CCRT or chemotherapy were not candidates for curative surgery. If there was a favourable response, GC patients with metastases to the liver, lungs, or bones would have surgery. After receiving neoadjuvant CCRT or chemotherapy, conversion to surgery will be carried out. Age, sex, tumour size, depth of invasion, lymph node metastasis, clinical TNM status, vascular invasion, perineural invasion, tumour location, histological tumour differentiation grade, pre-treatment metastasis site, and pre-treatment serum carcinoembryonic antigen (CEA) level are some examples of clinic pathological characteristics that were examined. Since trastuzumab was not covered by insurance in Taiwan, Her-2 expression testing was infrequent. Her-2 expression was not regularly checked for neoadjuvant setting in the current investigation because Her-2 expression was only 6% positive there as well. The purpose of this study was to compare preoperative CCRT to preoperative chemotherapy for treating locally progressed or metastatic GC [8].

The multimodal therapeutic toolbox currently has no

recognised superior neoadjuvant procedure on a global scale. Strong interinstitutional discrepancies regarding the order of radiotherapy and chemotherapy for the treatment of patients with locally advanced T4 or metastatic GC stem from the ambiguous interpretation of trial outcomes. It is still unclear whether preoperative chemotherapy or CCRT ought to be suggested for the care of individuals with locally advanced T4 or metastatic GC. The National Comprehensive Cancer Network-supported recommendations also recommend both of these alternatives. Based on actual patient data from one institution and a review of the recent literature, we compared the survival data of patients with locally advanced T4 or metastatic GC treated with either CCRT or chemotherapy [9].

Discussion

The GC is still one of the most common malignant tumours worldwide, according to our prior studies. Treatment for people with locally advanced or metastatic GC has not significantly evolved over the previous few decades. When surgical care is linked to considerable morbidity and difficulties that can prevent early adjuvant therapy, a neoadjuvant strategy may increase the likelihood of finishing multimodality therapy. A well-established primary treatment option for various gastrointestinal malignancies, such as rectal and esophageal cancer, is preoperative concurrent chemo radiotherapy (CCRT). Sterilization of the surgical site is a component of this treatment strategy, which may lessen the possibility of local tumour propagation during resection. Smaller and more precise radiation treatment fields would also be possible with preoperative CCRT, which might enhance chemotherapeutic effects and treatment toleration. Neoadjuvant radiation offers some additional, noteworthy benefits when given to individuals with unremarkable locally progressed or metastatic GC. Planning treatments is made easier and there may be less harm to surrounding organs when there are intact tumours and preserved normal anatomy. Adjuvant radiation, in contrast, calls for high doses and sizable treatment fields, which could exacerbate toxicity [10].

Neoadjuvant therapy can be used widely, although its benefits can be more noticeable in these particular patient categories. Individuals treated with neoadjuvant CCRT have shown greater response rates in prospective studies than patients treated with chemo radiotherapy alone. Numerous clinical trials have demonstrated the viability of neoadjuvant CCRT and the fact that resection rates are higher in CCRT-treated patients. Trials investigating ways to enhance preoperative treatment approaches for locally advanced or metastatic GC are expected to produce a wide range of findings. To obtain better local control, radiation is frequently added to preoperative chemotherapy. Following chemotherapy, radiotherapy may lessen the tumour's fibrous adhesion and focal inflammatory edoema. Neoadjuvant CCRT drastically decreased loco regional recurrence from 34% to 14%, with only 1% of cases occurring in the field, according to a recent phase III clinical research. After neoadjuvant CCRT, there was no local recurrence in a Japanese pilot study [11].

The current study showed that patients with locally advanced or metastatic GC treated with CCRT had favourable OS and PFS outcomes. Of the 65 patients in our study, 18 (27.7%) fell into the response group, whereas the remaining 47 (72.3%) fell into the nonresponse group. According to the study's findings, individuals who received neoadjuvant CCRT for locally advanced or metastatic GC tended to have longer PFS and OS than those who had neoadjuvant chemotherapy alone. Between the two therapies with acceptable toxicity and safety, we found no difference in the morbidity rate. Our study has a number of drawbacks. First of all, the sample size for this study was somewhat tiny. Neoadjuvant CCRT outperformed neoadjuvant chemotherapy alone in terms of OS and PFS, but no appreciable improvements in toxicity, response rate, disease control rate, or respectability were found.

The use of neoadjuvant CCRT in the treatment of patients with locally progressed or metastatic GC was therefore supported by these findings. These results need to be confirmed by subsequent research with larger sample sizes and meticulous patient monitoring. To correctly select patients for multimodal treatment, more research with specialised designs are required as well as trustworthy biological indications of genuine functional state. Such research's findings might be utilised to persuasively show that treating patients with locally progressed or metastatic GC is therapeutically effective [12].

Conclusion

Our findings demonstrated that candidate ADC targets with potential for translation across various tumour types can be found and prioritised through HPA mining. Therefore, this extensive antibody-based analysis may aid in selecting the targets for more research and, in turn, aid in the creation of new, clinically viable, and secure ADCs in the near future.

Conflict of Interest

None

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None

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