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Clinical Applications of RNA Editing Technology for the Early Detection of Cancer and Future Directions

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Abstract

Early detection of cancer has great clinical importance and potentially improves cure, survival rate and treatment outcome. RNA editing technology can be used as targeted and precise molecular scissors to cut and replace disease-causing genes with healthy ones. This is a post transcriptional modification that can lead to the recoding of proteins. RNA editing technology is in its infancy, but it can be used for early diagnoses and effective treatment of cancer. The full potential of precision medicine will be achieved by using the knowledge of RNA reversible-recoding to edit the protein. RNA editing technology could be used to expose chemo resistant cancer cells, dormant cancer stem cells and other malignant tumors. RNA editing generates RNA and protein diversity to accelerate and enhance the screening window for early detection of cancer. We propose that the RNA editing sites could be used as a novel tool for early detection of cancer.

RNA Editing and Clinical Applications

Cancer is one of the leading causes of death worldwide.[1] There is currently no cure and early detection of cancer offers the opportunity for greater treatment outcome and cure.[1] Innovative new technologies are being developed to aid in the early detection of cancer and treatment.[1-3] The use of RNA editing technology for prediction, diagnostics and treatment of cancer is expected to enable more precise, and preventive clinical care.[4-6] The RNA editing platform enables discrimination between normal and cancerous cells (Figure 1).[4,7,8]

Researchers are focusing on the development of RNA editing sites, which has the potential to detect cancer at early stage.[9,10] Published studies have indicated the role of ADAR2 (adenosine deaminase acting on RNA 2) and APOBEC1 (apolipoprotein B mRNA editing catalytic subunit 1) in cancer detection, and their use in predicting the survival of cancer patients.[5,6] The ADAR1 and 2 are part of the spliceosome, which is expected to regulate effectiveness of RNA editing and splicing machinery.[11] ADAR2 is also able to edit its own precursor mRNA to generate new splicing sites, control stability and decision-making process of other editing sites.[7] ADAR enzymes target non-coding microRNAs (miRNAs), which can be used not only to correct tumor-specific mutations but also to expose tumors antigens to immune system.[11] Mis-regulated RNA editing can promote the progression and metastasis of cancers.[7] For example, antizyme inhibitor 1 (AZIN1) is overexpressed in hepatocellular carcinoma. In cancer development misguided ADAR2 suppresses immune sensors (MDA5 and PKR), thereby promoting tumor growth.[5,11] Correctly regulated editing sites by ADAR2, activates the immune system and leads to suppression of tumors.[5] Clinically relevant editing sites could be identified and can be used for early detection of cancer.[7] For instance, editing site I342M can be used for detection of breast cancer and editing site S367G can be used for diagnosis of hepatocellular cancer.[5,11] APOBECs are well known for their ability to edit proteins and miRNAs in different diseases and cancer.[12,13] APOBEC1 protein regulate hypermutations in cancers and might affect expression levels of cancer genes.[12,14] APOBEC1 expression has been linked to cancer and could be used for early detection of cancer.[5,12] For

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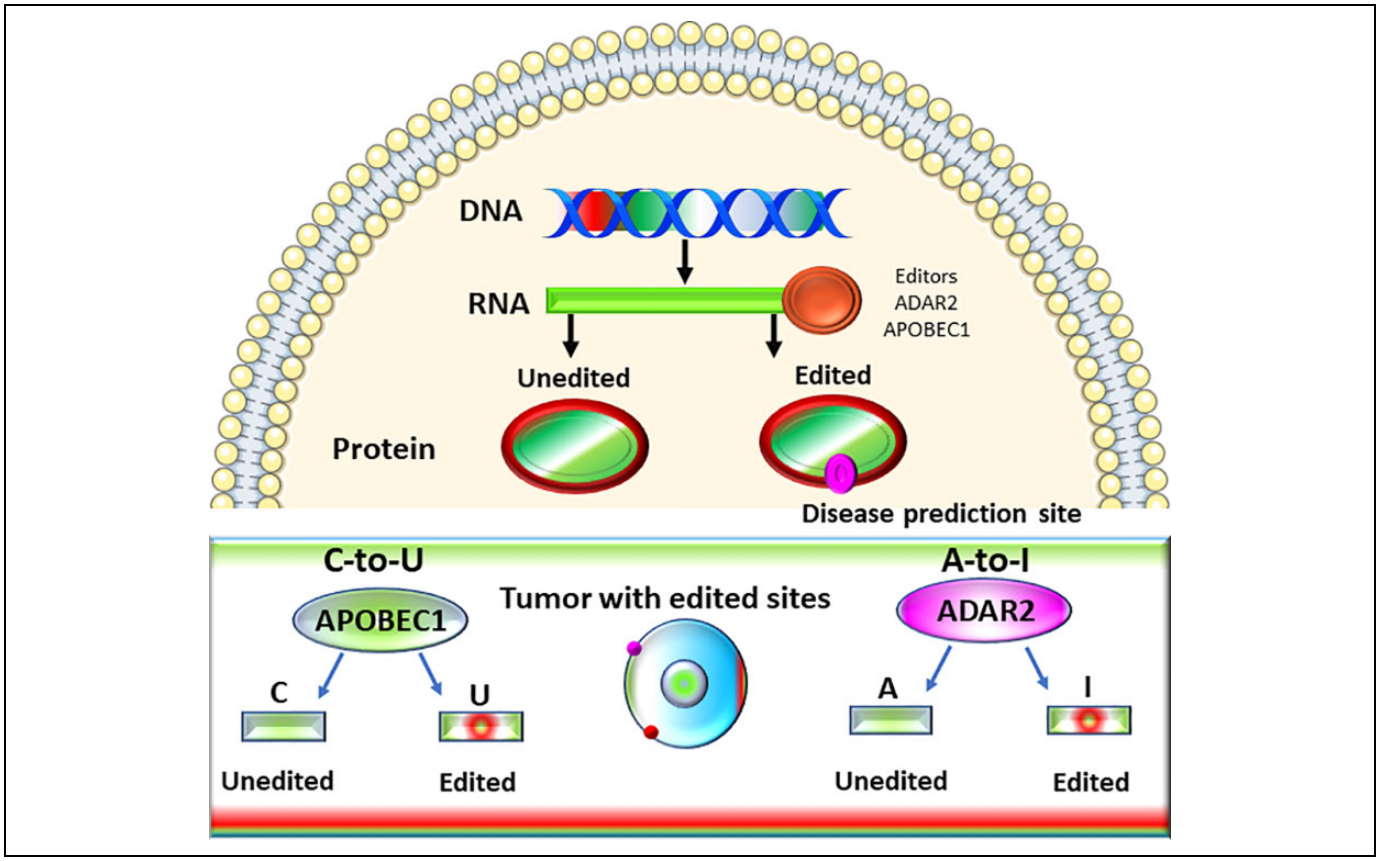

Figure 1. Schematic diagram of RNA editing technology in early detection of cancer and other diseases.

instance, unregulated RNA editing of APOBEC1 induce somatic mutations in esophageal cancer.[12,13] The discovery of APOBEC1, together with its cofactor RBM47, has led to the identification and validation of hundreds of RNA editing sites, which can regulate the immune system.[5,13] Cytosine to uracil (C-to-U) editing, mediated by APOBEC1, is an important new avenue to be studied and may promote a more aggressive phenotype in cancer progression.[13] The use of new technologies such as RNA editing and imaging techniques have significantly improved, early interventions for cancer.[2,4] The improvement of RNA editing technology allows detecting cancer sooner for more precise prediction and treatment of cancer with greater specificity.[5]

Genome editing technologies are rapidly emerging and becoming more important in clinical and translational medicine.[4,5] RNA editing, the post-transcriptional recoding of RNA molecules, has the potential to ultimately elucidate biological mechanisms behind disease development and progression.[4-6] Clinical trials of RNA editing therapy are on the way to evaluate for its efficacy in different diseases and especially for cancer.[4-6] The genome contains all the necessary information that dictates cellular processes and physiological functions.[15] RNA editing is an important stepping stone for clinicians to learn more about cellular processes of cancer.[15] RNA editing technology plays an important role in fine-tuning biological function and opens novel opportunities to treat many diseases including cancer.[4,15]

Whether clinical trials of cancer treatment succeed or fail, we need to reevaluate the lessons learned from previous trials and it is essential to understand the biological concept of RNA editing when moving forward toward the clinics.[14,15] In the flow of genetic information from DNA to protein, RNA works as a messenger between DNA and protein.[8,15] RNA receives the DNA-dictated message and sends it further for protein production.[14] Due to its central role in biological information, RNA editing technology has attracted much excitement to fix mutated genes in cancer and treat other diseases by fixing faulty genes by recoding of nucleotide sequence (Figure 1).[4,5,14] RNA editing is reversible, and by reprogramming editing sites it is possible to rewrite the gene information.[10,14] Unlike DNA editing and CRISPR technology, which is permanent for genome editing, the effects of RNA editing are reversible and temporary.[14,16] This technology opens a new gateway for treating temporary conditions of pain, inflammation, and permanent condition of gene mutation and other diseases.[14,16] Scientists are developing novel RNA editing therapies by designing new RNA editors, and engineering new molecules that guide editor enzymes to specific edit sites.[4,16]

Emerging Technology of RNA Editing

RNA is a working copy of DNA that acts as a messenger to carry information between DNA and the cellular machinery to

make proteins (Figure 1).[1,15,17] Many genetic diseases are caused by mutations in RNA, therefore scientists recently developed **R**NA **E**diting for **P**rogrammable **A** to **I** **R**eplacement (**REPAIR**) system to test whether editing technology can be used to fix such mutations.[17] The **REPAIR** system has the ability to recognize, cut and edit RNA sites.[17] It could open up new therapeutic options for early detection of cancer and other diseases by enabling recoding of RNA and then rewriting the protein to correct the faulty sites.[4,15] The ability to correct disease-causing mutations by efficient and precise recoding is one of the primary goals of RNA editing.[15,17] Recent studies have associated RNA editing with cancer development which can be used for diagnosis and treatment of cancer.[15,17] Even though RNA editing is associated with cancer development, the function and clinical relevance of editing in cancers have not been well studied.[5,16] This new technology opens up new opportunities to recover the function and treat many diseases.

The new emerging platform of RNA editing would provide biological understand of the chemo resistant cancer and possibilities for re-designing new drugs.[17] RNA editing could be helpful in improving initial detection of cancer and developing more predictive biomarkers in cancer patients. The publicly available database of **DARNED** (**DA**tabase of **RN**A **ED**iting) provides centralized access to available published data related to RNA editing.[4,6,17] **RADAR** (**R**NA-editing **A**nalysis-pipeline to **D**ecode **A**ll twelve-types of **R**NA-editing events) is another database to detect and visualize RNA editing events.[8,17] EDK (Editome Disease Knowledgebase) can be used to identify RNA targets, editing sites, associated proteins, and other intermediate regulators, suppressors and activators for RNA-editing machinery.[11,18] EDK is as an open access resource and is helpful to understand editome-disease associations and the regulators of RNA editing machinery.[18] These databases have been designed for researchers seeking information on RNA editing and can be used for bioinformatic hunting to search and identify RNA editing sites in different diseases. RNA editing can be used to fix the genetic mutation in cancer.[5,7,9] None of the RNA editors are perfect yet.[14] It is also unknown whether mis-regulation of RNA editing in a particular disease is a cause or a consequence. However, the designing of new drugs based on RNA editing technology, will only contribute to curing the disease if mis-regulation is the cause.[18] Understanding the precise role of RNA editing remains a challenge and needs further study to explore its role in different diseases.

Conclusions

Reprogrammable RNA editing technology has the potential to reversibly recode and rewrite the RNA information for research and disease treatment.[15,17] RNA editing can be used to unravel dormant cancer stem cells that often escape chemotherapies.[9,10,14] In this way RNA editing could be used to target therapeutic resistance and tumor relapse. We propose that engineered-guided-RNAs that bind ADAR and direct it to fix RNA mutations would bring new opportunities to identify cancer biomarkers at early stage.[10,14,19] Using RNA editing sites as a tool, many early events in cancer progression can be identified.[4,17] Understanding the precise role of RNA editing remains a challenge and needs further study to explore its role further. Still, many open questions remain. For instance, Do ADARs contribute to human diseases independently of RNA editing? Is it possible to target and correct RNA misediting sites? How do editor enzyme-sensors distinguish between good and bad sites? How many RNA editing sites are transferred to next generation? Although there are considerable hurdles to overcome, we will likely see RNA editing technology in clinical trials in the future as a novel therapeutic approach.

Future Directions and Challenges

RNA editing is currently changing the frontiers of medicine and offers benefits over genome and germline gene editing, which alters the genome at its earliest stages, and may affect every cell of the organism.[15,17] The ability to predict and diagnose cancer at an early stage, the RNA editing can achieve this with lower error and more precision, although the technology is certainly not yet perfect.[17] Along with ethical concerns there is no clear consensus as to whether RNA editing is just an incremental step or disruptive step moving forward for clinical translation.[7,17] RNA editing is a very powerful strategy for precise manipulation of cells but it requires further study to overcome the difficult technical challenges of editing sites and editor enzymes.[17] There are certainly potential benefits, risks and harms associated with this technology. The biosensing and bioengineering are new approaches that can improve this technology further by designing new editor enzymes that target RNA, and can be used to correct faulty proteins in different diseases, genetic and non-genetic conditions.[10,17]

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