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Mutated isocitrate dehydrogenase and therapeutic modalities

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Abstract. Isocitrate dehydrogenase (IDH) is crucial in the metabolism pathway that converts isocitrate to α-ketoglutarate. When isocitrate dehydrogenase is mutated, IDH produces 2-hydroxyglutarate instead of alpha-ketoglutarate. The newly formed IDH, with the ability to dysregulate the metabolic pathways of cells, can potentially lead to the development of cancer. The mutation leads to malignancies such as acute myeloid leukemia and glioma. Current treatment for IDH-related malignancies includes IDH inhibitors, epigenetic modulators, immunotherapies, and cancer vaccination. The development of a cancer vaccine requires the discovery of a suitable epitope being found. Newly developed deep learning algorithms have the ability to predict protein structures and thus have the potential to help discover suitable epitopes for cancer vaccines. This study discusses the structure of IDH and gives an overview of how mutated IDH can potentially cause malignancies. In addition, this study proposed potential approaches with deep learning to aid the investigation of preventing IDH using cancer vaccines.

Keywords: isocitrate dehydrogenase, acute myeloid leukemia, glioma, deep learning, cancer vaccine.

1. Introduction

Acute myeloid leukemia (AML) is classified as a serious, and lethal disease. It is caused by a genetic mutation in which the mutated gene impairs the proliferation of white blood cells. Approximately one-third of all diagnosed leukemias are AML [1]. Glioma is a kind of primary brain tumor that arises from the glial tissues and consists of astrocytomas, oligodendrogliomas, and glioblastomas [2]. One dehydrogenase commonly found in AML and glioma is Isocitrate Dehydrogenase (IDH), which occurs in up to 30% of all AML cases and 80% of the gliomas that are recognized as the World Health Organization (WHO) level II and III cases [3]. Both of these malignancies remain fatal. AML patients that are under 40 years of age have only 28% of the 5-year survival rate. In contrast, the most lethal type of glioma (GBM, which is Health Organization grade IV glioma) has the 5-year survival rate less than 5% [4-5]. Improving the five-year survival rate for glioma and AML becomes critical. As IDH mutation is commonly found in AML and glioma patients, understanding the mechanism of IDH impacts cancerogenesis can help develop therapies for treating AML and glioma. The current investigation of IDH focuses on the mutants of IDH, IDH1, 2, and 3. Studies have shown that mutated IDH generates 2-Hydroxyglutarate (2-HG), which dysregulates the DNA methylation and metabolic pathway of a cell [3]. Since the significance of the appearance of 2-HG, studies have also been focusing on inhibiting 2-HG production. These studies have shown the possibility of using 2-HG inhibitors to reduce the lethality of IDH-related cancer [3]. Other studies, such as using immunotherapy to treat IDH-related glioma, also

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showed the validity and its ability to reduce the tumor volume and elongate overall survival [3]. This study proposed two potential directions for treatments and preventions for IDH-related malignancies. Schumacher et al.'s research has shown the potential of preventing IDH-related malignancies through cancer vaccination [6]. The study mainly focuses on the IDH1-R132H mutation; another vaccine for preventing different variations of IDH mutation, such as IDH2-R172 mutations, still remains undiscovered. In addition, AlphaFold, with its ability to predict protein folding and structure precisely, has shown potential in aiding the development of target medicines targeting IDH-related malignancies.

2. Mechanism

2.1. The normal function of IDH

Isocitrate Dehydrogenase enzyme, or IDH, is crucial in catalyzing the oxidation decarboxylation reaction of isocitrate. There are three kinds of IDH enzymes. IDH1 locates within cytoplasm and peroxisomes. In contrast, mitochondria are where IDH 2 & 3 appear. IDH 1, 2 & 3 are catalyzers of isocitrate to α-ketoglutarate (α-KG), which also known as 2-oxoglutarate (2OG). The catalyzation with IDH1 & 2 requires nicotinamide adenine dinucleotide phosphate (NADP+) involve. As the product of the reaction, NADPH is produced. IDH3 requires nicotinamide adenine dinucleotide (NAD+) involve. NADH is the product of the reaction. NADP+ is another coenzyme crucial to metabolism [7]. It is good to note that the catalyzation of IDH 1 & 2 is reversible, while the reaction of IDH 3 is not. While all three kinds of IDH are responsible for catalyzing isocitrate into α-KG, their purpose remains to differ. IDH1 is known to participate in reactions related to metabolizing lipids and detecting glucose levels. In contrast, IDH2 is mainly included regulating the celluar respiration. IDH3 converts isocitrate to α-KG irreversibly [8].

2.2. IDH Molecular structure

IDH1 & 2 are homodimeric enzymes which means they are composed of two identical subunits. Each dimer of IDH1 & 2 contains large, clasp, and small domains. In human IDH1, the structure is composed of two non-adjacent segments of amino acids in the large domain, which are 1-103 and 286-414. Meanwhile, the clasp region is made up of amino acid residues 137-185. The small domain comprises amino acid residues 104-136 and 186-285 [8]. IDH 3 is a heterotetrameric enzyme, meaning that it is composed of four unidentical subunits [3].

2.3. The effect of mutated IDH

IDH1 and IDH2 appear to be very important to the growth of cancers. For example, gliomas, and acute myeloid leukemia (AML). These are lethal cancers that can have a serious effect on a patient. Mutated IDH1 & 2 disrupt the normal metabolism pathway. With the production of 2-HG, the reprogramming of metabolism takes place [3]. The high expression of 2-HG is also found to be related to the increase in histone methylation and the pause in cell differentiation. A decrease of α-KG is led by the catalyzation of α-KG to 2-HG. A decrease in the density of α-KG prevents the hypoxia-inducible factor 1-alpha (HIF-1α) from decomposing, and also helps with the formation of new blood vessels, which contributes to the growth and spread of tumors [9]. Mardis et al. also found that IDH mutation frequently appears in AML victims [10]. IDH1 and IDH2 mutations appear in around 20% of the AML patients according to studies. 6-16% of the AML patients are found to have IDH1 mutation. 8-19% of the AML patients are found to have IDH2 mutaion. Older people have a higher risk of having an IDH-mutated type AML.

2.4. Mutated IDH led to the production of 2-HG

A increase in 2-HG level is led by the mutation of IDH, which positively affects the formation of cancer. In IDH1, the mutation is normally R132, while R172 residue mutation is normally found for IDH2. The mutated residue reduces the affinity IDH has for isocitrate and therefore affects the recognition of isocitrate. The mutated IDH1 gene produces two types of IDH1 monomer, a wild-type one and a mutated one. The IDH1 homodimer with two wild-type monomers transforms isocitrate into α-KG. The IDH1

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with heterodimer comprises an R132-mutated monomer, and a wild-type monomer transforms α-KG to 2-HG. However, the enzyme comprised of two R132-mutated monomers is inactive [11].

The mutation of IDH1 can change the arginine of the active site, most commonly for R132C, R132H, R132L, or R132S residues [12], which corresponds to the different replacement of arginine into four kinds of amino acids at position 132 of the polypeptide chain. In grade II and grade III gliomas as well as the secondary glioblastoma in human, the R132H mutation is the most commonly found. Also, the gliomas relating to mutated IDH have a clinical and genetic difference from gliomas with wild-type IDH genes. According to studies, in the early stage of glioma, IDH mutation is found positively related to its development [11].

The most commonly discovered mutations of IDH2 are the IDH-R140 and IDH2-R172. In acute myeloid leukemia, a large amount of victims suffer from IDH2-172 mutation [12]. IDH2 mutation occurs slightly higher than IDH1. As previously mentioned, the expression of 2-HG was found to be related to histone methylation. To be more specific, a model system suggested by Kernytsky et, al. has shown that the expression of IDH2 mutation can cause changes in DNA methylation change, and a change in histone [13]. Research conducted by Green et al. also shows that different IDH mutations produces AML with different effects. Victims has a IDH2-R172 mutant had palpably fewer white blood cells than those with IDH2-R140 mutation. In addition, they also have a higher risk of having an abnormal karyotype. The study also shows that various types of IDH2 mutation react differently to therapies [12].

Treatment for Glioma and AML contains similar treatments as these cancers share the basic pathogenic mechanism: mutated IDH leading to the production of 2-HG, which, when 2-HG functions abnormally, leads to cancerogenesis. Most ongoing research focuses on targeting the 2-HG function and its correlation to other molecules.

2.5. Treatments in glioma

Treatment research for IDH-mutant glioma includes treatments that target the mutated IDH, epigenetic modulators, DNA repair enzymes, essential metabolic enzymes, redox homeostasis, and immunotherapies [3]. Rohle et al. discovered AGI-5198, a man-made substance that stops IDH mutant from making 2-HG [14]. Ivosidenib (AG-120) and vorasidenib (AG-811) are second-generation inhibitors. Ongoing clinical studies focus on their safety and effectiveness on IDH-related malignancies such as glioma [3]. Epigenetic modulators are newly derived treatments for IDH-mutated cancers. The IDH mutation may cause hypermethylation, resulting in a broad epigenetic alteration in tumor cells. Correcting dysregulation is a potential therapeutic strategy approach for treating cancers that are related to mutated IDH [15]. 2-HG produced by IDH mutant interferes with DNA repair enzymes and impairs DNA repair pathways. This causes the IDH-mutated cells to utilize PARP-mediated BER for DNA damage repair [16]. Suppressing BER of IDH-mutated cells and therefore causing the destruction of target cells can be a potential treatment for IDH-mutated glioma patients. Studies have shown the effectiveness of PARP-repression-type therapy [3]. In patients with IDH-mutated glioma, NAD is synthesized mainly by salvage pathways. This means blocking the salvage pathways of IDH-mutated glioma can be a potential therapeutic target [17]. Studies and clinical trials also show another potential therapeutic target for killing glioma and AML cells by inhibiting glutamine metabolism [3]. The elevation of reactive oxygen species appears to be another characteristic of IDH-related cancer [18]. The elevation of ROS burden the cancerous cells to use glutathione for scavenging ROS. Targeting fragile redox homeostasis of these cancerous cells can potentially treat IDH-related glioma [3]. Immunotherapy shows its potential in treating IDH-mutated glioma. The excess of 2-HG results in a suppression of T-cell receptor signaling that requires ATP to involve. This result leads to the inhibition reproduction as well as the gathering of CD8+ T cells in the area affected by the tumor [3]. Inhibiting the function of 2-HG, and thus helping with the T-cells proliferation, can reduce the tumor volume and extend overall survival time [19].

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2.6. Treatments in Acute Myeloid Leukemia

Treatment research for IDH-mutant AML includes induction chemotherapy, hypomethylating agents (HMAs), and small-molecule mutated IDH inhibitors [20]. This study focuses on IDH-related therapy, which is (HMAs) and small-molecule mutated IDH inhibitors. Hypermethylation is significantly shown in the IDH1 & 2 mutated related myeloid malignancies; therefore, treating it with HMAs for IDH1 & 2 mutated AML can be a potential treatment. However, the result shows that the effectiveness of using HMAs to treat IDH1 & 2 mutated AML is still equivocal [20]. As the characteristic of mutated IDH1 & 2 is transforming α-KG to 2-HG, blocking or reducing the transformation of α-KG to 2-HG becomes a possible treatment for AML that has a positive relation to IDH. The mutated IDH inhibitors include AG-120, enasidenib (AG-211), AG-881, IDH305, and FT-2102 [20]. AG-120 targets IDH1-R132 mutation. The study has shown that AG-120 is valid for reducing the level 2HG into a healthy range [21]. The overall response rate for this treatment is 35% in which 78% of the victims have R/R AML [20]. Enasidenib inhibits abnormal enzyme produce by IDH2-R140 and IDH2-R172 mutation. Similar to AG-120. Enasidenib also reduces the 2-HG level to a healthy range [21]. AG-881 can inhibit both IDH1 mutant and IDH2 mutant and is being assess for use in the tumor in phase 1 [20]. IDH305 and FT-2102 are drugs that inhibits IDH1 mutant, both under investigation in phase 1; until this paper is written, NCT02381886 clinical trials still have no data posted.

3. Suggestion

3.1. Vaccination for IDH mutation

Vaccination is a potential treatment and prevention for IDH-mutated related cancer. Cancer vaccination aims to cause an immune response to synthetic antigens, causing T-cell responses [22]. A study conducted by Schumacher, T et al. has shown that IDH1 mutation, specifically IDH1-R132H has the potential to produce a cancer vaccine. It contains an epitope usable for mutation-specific vaccination. It presents peptide with the help of histocompatibility complexes (MHC) class I. This presentation can lead to CD4(+) T-helper-1 (TH1) responses that are specified for this mutation. Then, the CD4(+) TH1 cells as well as the antibodies can recognize victims with IDH1-R132H mutation, therefore, causing an immune response. In addition, the T-cell is able to discriminate between the cell with wild-type IDH1 and the cells with mutated IDH1 [6]. Though this study only discovers the potential of peptide vaccine for IDH1-R132H mutation, discovering a more approachable peptide vaccine for different kinds of IDH1-R132 mutation seems applicable. Furthermore, as IDH2 was similar to IDH1 [3], using a similar strategy to find a suitable epitope for production seems promising. In addition, deep learning has shown its potential for predicting T cell receptor (TCR) epitope binding [23].

3.2. Deep learning and IDH

Deep learning has the potential to recognize and discover new targets for treating IDH. Deep learning offers a powerful tool for analyzing large datasets and identifying potential therapeutic targets. Deep learning helps with recognizing the stage of the glioma patients that have IDH mutation. Choi, Y et al. used Convolutional Neuron Network (CNN) for evaluating the stage of glioma patients using the Magnetic Resonance (MR) image [24]. Deep learning can also be used to analyze the gene expression data of IDH-mutated gliomas, which can help identify new targets for treatment and predict the patients who may benefit from certain therapies [25]. A study has used deep learning to understand the biological pathways of IDH. The analytical ability of deep learning shows its potential for evaluating large datasets of patient data, which can be used in finding similarities among different phenotypes of cancers and inspiring the development of new drugs. For example, The Cancer Genome Atlas program has collected large-scale genomic and proteomic datasets from different kinds of cancer, including IDH-mutated gliomas. Using this large dataset for training deep learning models, researchers can develop more accurate and generalizable models to guide and inspire drug discovery [26]. Research conducted in 2021 also shows the potential of using deep learning algorithms to predict the protein structure [27]. This ability to predict the structure of protein gives another approach to the discovery of new targets.

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In conclusion, newly developed technologies such as cancer vaccination and deep learning are two promising approaches for preventing, recognizing, and treating IDH-mutated related cancer. Cancer vaccination showed its potential by inducing immune responses with synthetic antigens and causing T-cell responses for animals with IDH1-R132H mutation glioma. Deep learning has shown its potential to identify potential therapeutic targets for IDH-mutated gliomas, as well as IDH mutation status recognition. Despite the potential of vaccination and deep learning, challenges still need to be addressed. For cancer vaccination, more suitable epitopes needed to be found for different kinds of IDH mutations. We can see the difficulty of identifying suitable epitopes by the fact that only IDH1-R132H mutants found suitable epitopes for producing cancer vaccines. When it comes to deep learning, collecting large amounts of high-quality data requires effort. Due to the differences in equipment in different areas, the data may be hard to obtain. Also, the reliability of datasets also needs a human to validate, which, when it comes to a huge dataset, the time and cost for training a model become high.

4. Conclusion

This study discusses the pathogenic mechanism of Isocitrate Dehydrogenase (IDH) and the current progress of treatments for different malignancies caused by various IDH1, 2, or 3 mutations and proposes two new directions of studies that are beneficial to the treatment of IDH-related malignancies. The IDH mutation has shown a significant association with cancerogenesis. IDH is presented in the cytoplasm and mitochondria. It works by catalyzing the transformation of isocitrate into α-ketoglutarate. They are a critical-metabolic molecules involved in Krebs cycle. IDH1 and IDH2 require nicotinamide adenine dinucleotide phosphate (NADP+). IDH3 requires nicotinamide adenine dinucleotide (NAD+). Catalyzation of IDH1 and IDH 2 is reversible, while the catalyzation of IDH 3 is not. The mutated IDH leads to the production of 2-hydroxyglutarate (2-HG). 2-HG is able to disrupt the metabolic pathway of cellular respiration and dysregulate DNA methylation. This change contributes to cancerogenesis. Acute myeloid leukemia and glioma are two severe, lethal, and widespread cancers that are found to be associated with IDH. The reprogramming of metabolic pathways contributes to the metastasis of cancer. Currently developing treatments include synthetic inhibitors, epigenetic modulators, DNA repair enzymes, targeting essential metabolic enzymes, targeting redox homeostasis, and immunotherapies. These treatments have shown promising results in inhibiting the metastasis of tumors. The IDH1 R132H vaccine is another approach to treating IDH-related cancers. However, discovering suitable epitopes for producing vaccines requires time and opportunities. Deep learning, with the ability to simulate protein structure, has the potential to help the discovery of suitable epitopes for producing cancer vaccines. This study suggests that using computational technologies, particularly deep learning, can aid the development of treatments for IDH-related malignancies. Using deep learning to analyze complex datasets and meaningful patterns and associations, researchers may be able to gain new insights into the mechanism underlying cancers and discover potential treatments for this cancer. In Addition, the AlphaFold provides the possibility to predict the structure of proteins, which may be beneficial to the discovery of potential targets. Meanwhile, collecting high-quality and reliable data is another challenging problem that remains unsolved. This study did not show the availability of using deep learning to aid the discovery of new targets. Future studies can focus on using deep learning in the recognition of possible treatment targets for IDH-related cancers.

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