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Targeting Riboflavin Receptor 3 in Neurological Diseases

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1. Abstract

Neurological diseases are widespread and serious global illnesses. Neurons highly rely on aerobic metabolism in mitochondria. Riboflavin receptor 3 (RFVT3) is a vital section of the mitochondrial network, which plays a key role in riboflavin homeostasis and the production of adenosine triphosphate (ATP). The abnormal expression of RFVT3 is closely associated with the occurrence and progression of multiple neurological diseases. Therefore, it is crucial to explore the dynamic expression of RFVT3 for the diagnosis and treatment of neurological diseases.

The brain function critically depends on aerobic metabolism in mitochondria [1]. The dynamic regulation of the mitochondrial network plays a vital role in ensuring energetic demands to maintain neuronal and axonal energy homeostasis. Therefore, reprogramming of mitochondrial energy metabolism is a central aspect of multiple neurological diseases, including glioma, stroke, Alzheimer's, Huntington's, and Parkinson's diseases [2].

Riboflavin receptor 3 (RFVT3, encoded by the SLC52A3 gene) was named RFT2 previously and identified in 2009 [3]. RFVT3 is a vital section of the mitochondrial network, which is a key protein in mitochondrial energetic metabolism reprogramming and plays a significant role in riboflavin homeostasis. Riboflavin (Vitamin B2) is an essential micronutrient in energy production. The active forms flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) act as either coenzymes or prosthetic groups in a wide diversity of biochemical reactions, such as electron transportation, ATP production, RNA inhibition, DNA repair, and protein folding. Therefore, the abnormal expression of RFVT3 and/or the metabolic disturbance of riboflavin is closely related to a series of diseases, such as nervous system diseases [4], cancer [5], immunological diseases [6], and cardiovascular diseases [7].

Molecular imaging especially nuclear medical imaging can demonstrate how specific proteins or pathways function in their native context, thus contributing to a systems-level understanding of biology and having the potential to guide the

early diagnosis, precise treatment, and disease risk assessment [8]. RFVT3 has been identified as a potential biomarker for nuclear medicine and molecular imaging. To the best of our knowledge, we first report a series of RFVT3-targeting positron emission tomography (PET) and single-photon emission computed tomography (SPECT) probes for imaging neurological diseases, such as glioma and stroke [9, 10].

In a previous report, Fu et al found that RFVT3 was significant overexpression in human glioma compared with normal brain tissue. The expression of RFVT3 was closely correlated with WHO grade ($P < 0.001$) [11]. Considering the importance of riboflavin and its derivatives (FMN and FAD) in metabolic activities, it is clear that monitoring such metabolic activity with molecular imaging probes is highly desirable. We first utilized the click chemistry approach to synthesize a novel PET tracer for imaging RFVT3 [10]. IC_{50} measurement validated the efficacy of the modified riboflavin. *In vivo* PET imaging further demonstrated that a new ^{18}F-labeled probe (^{18}F-RFTA) could be used to provide high-contrast tumor imaging. In addition, a number of studies have shown that RFVT3 is important in the development of several cancers, including cervical cancer [12], gastric cancer [13], and esophageal squamous cell carcinoma [14]. We envision that the new target/probe system may be leveraged for extensive use in the diagnosis and treatment of RFVT3 overexpressing cancers.

In addition, RFVT3 is a potential target for the early diagnosis and effective treatment of ischemic stroke. The patients with acute ischemic stroke were administrated high dose riboflavin demonstrated a decrease in excitotoxic damage and consequently clinical improvement in a clinical phase II trial [15]. Our studies found that RFVT3 was overexpressed in the infarcted brain tissue after ischemic stroke compared with normal brain tissue in rat MCAO models [9]. We first radiosynthesized an RFVT3-targeted SPECT probe ^{131}I-riboflavin (^{131}I-RFLA) for imaging the ischemic stroke *in vivo*. The SPECT/CT images demonstrated a high ratio of infarcted brain to normal brain, which was identified by H&E and immunohistochemistry staining *ex vivo* [9]. We concluded that RFVT3 is a potential biotarget for imaging stroke-related mitochondrial metabolic reprogramming.

Brown-Vialetto-Van Laere (BVVL) syndrome is a neurodegenerative disease characterized by progressive ponto-bulbar palsy, muscle weakness, and amyotrophy [16]. BVVL patients with RFVT3 mutations showed a decreased riboflavin level in plasma. Supplementation of high-dose riboflavin significantly improved the clinical symptoms and the biochemical abnormalities in BVVL patients [17]. Therefore, RFVT3-targeting molecular imaging may be a potential strategy to achieve an early diagnosis and guide the precise treatment of BVVL.

In conclusion, the new biotarget/probe system has great potential for use in the diagnosis and treatment of RFVT3 aberrant-expressed neurological diseases. The system can be also applied for the management of other RFVT3-related diseases, such as cardiovascular diseases and immunological diseases.

2. Author contributions

All authors have made intellectual contributions to the work.

3. Declaration of Competing Interest

The authors declare that they have no competing interests.

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