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Fetal Hemoglobin Reactivation: Exploring Natural Therapies for Beta-Thalassemia and Sickle Cell Anemia

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Abstract

Fetal hemoglobin (HbF) is a potent genetic modifier, and the γ-globin gene induction has proven to be a sustainable therapeutic approach for the management of β-thalassemia. In this study, we have evaluated the HbF induction ability of A. vasica in vitro and in vivo, and the identification of potential therapeutic compounds through a bioassay-guided approach. In vitro benzidine-Hb assay demonstrated strong erythroid differentiation of K562 cells by A. vasica extracts. Subsequently, an in vivo study with an aqueous extract of A. vasica showed significant induction of the γ-globin gene and HbF production. By examining the action mechanisms of the HbF-inducing agents, various studies have suggested that despite the ability of stimulating HbF production, the chemotherapeutic agents could not be practically applied for treating β- hemoglobinopathies, especially β-thalassemia, due to the their cytotoxicity and growth-inhibitory effect. Owing to this therapeutic obstacle, much effort has been put on identifying new HbF-inducing agents from the natural world with the combination of efficacy, safety, and ease of use.

Introduction

β-Thalassemia is an inborn monogenic defect of β-globin production in hemoglobin leading to excess accumulation of α-globin chain that affects membrane integrity of RBCs, causes premature death of erythroid cells, and results in chronic anemia. The mainstay of treating thalassemia includes lifelong blood transfusion and iron chelation. At present, bone marrow transplantation and gene therapy have also offered great curative potential in its treatment, but their clinical utility is limited. Moreover, the unavailability of these modalities to the common person in the least developed countries is also a pressing problem [1].

Natural products are historically proven therapeutic agents in β-hemoglobinopathies. Importantly, the utilization of natural HbF inducers in countries with a high prevalence rate of disease is more affordable as compared to other ways of treatment. Some reported HbF inducers from natural sources are resveratrol, mithramycin, rapamycin, curcuminoid, cucurbitacin D, cinchonidine, and quinidine. Yet, many of these are recently identified HbF inducing agents, and their therapeutic applications are restricted due to their carcinogenic and cytotoxic properties and require further clinical trials [2]. Therefore, the need for new HbF inducers especially from medicinal plants exemplified with enhanced efficacy and minimal side effects is highly sought after.

SCD is an inheritable autosomal recessive genetic blood disorder. It is characterized by the abnormal appearance of the red blood cells which are rigid and sickled. SCD is attributed to a point mutation at the coding sequence of the β-globin gene which causes the substitution of glutamate by valine in the glutamic acid at the sixth position of β-globin protein, and thus forming sickle hemoglobin. When incorporating into a hemoglobin tetramer.

HbS will polymerize inside the red blood cells under hypoxic condition, resulting in the alternation of the shape of red blood cells as well as their function. Currently, the clinical manifestation in β-hemoglobinopathies is blood transfusion and gene transfer therapy. However, long-term transfusion therapy may cause iron overload in patients from the gradual breakdown of transfused blood which may eventually result in cardiac failure and/or even death. Though the advance in iron chelation can help to remove excess iron in patients [3], the survival rate is greatly dependent on the iron chelation regimens .Allogeneic hematopoietic stem cell transplantation (HSCT) is one of the gene transfer therapies aimed at the underlying molecular causes of SCD and β-hemoglobinopathies. Several hundred SCD and thalassemia patients have successfully experienced HSCT with promising results.

In vivo and in vitro screening platforms

With the aim of determining the therapeutic potency of the novel inducing compounds and studying the underlying regulatory mechanism of the embryonic and fetal human globin genes expression, various in vitro and in vivo screening platforms have been widely utilized. Forin vitro models, there are six human cell lines carrying an embryonic-HbF phenotype; they are K562 human chronic myelogenous leukemia cells, M-TAT, NSMeg, OCIM1, OCMI2, and AS-E2, while K562 cell line is one of the most well-known and widely used screening platforms for HbF inducers [4].

The protein–protein interaction and docking studies revealed that compounds have direct implications in the activation of γ-globin genes, which is supported by the high index of scoring among selected proteins and higher binding affinities of lead compounds with the DNA binding factor and its recruited co-repressor complexes, which are involved in the silencing of HBG [5]. The docking process was validated through a validation procedure that applies the known inhibitor of HDAC2. Nonetheless, the AutoDock analysis for the predicted pathway needs further validation through MD Simulations, and confirmation through experimental setup is in consideration for the detailed mode of action of these compounds in HbF induction.

From these observations, we inferred the potential role of A.

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vasica and its major alkaloids in HbF-inducing ability, with normal physiological hematocrit counts and hemoglobin content in vivo, and hepato-renal protective effects of the extract explicating the non-toxic nature of A. vasica [6]. However, in regards to HbF induction, further studies are still desirable for the exact mechanism involved in A. vasica-mediated γ-globin gene expression, differential globin genes expression profiling, promoter activity involved in individual globin gene switching and expression, key transcription factors involved in reactivation of HbF in vivo, and biochemical and hematological profiling with long-term administration (up to 6 months) in the in vivo mice model to fully anticipate the pharmacological HbF-inducing effects and safety of this plant in clinical utilization for hematological diseases [7].

Natural remedies as HbF inducer

In recent years, scientists have conducted numerous studies in order to identify the natural remedies that could be possibly applied in treating β-hemoglobinopathies, including SCD and β-thalassemia, summarized in. The extract of Aegle Marmelos containing bergatene was found to be responsible for the activation of erythroid differentiation and HbF induction in human leukemic K562 cells [8]. Citropten and bergatene are the active ingredients in bergamot juice. They are powerful inducers of erythroid differentiation, γ-globin gene expression and HbF synthesis in human erythroid cells. Thus, it is known as a potential therapeutic approach for both β-thalassemia and sickle cell anemia. In addition, Nicosan, an ethanol/water extract from Nigeria indigenous plants, has successfully demonstrated a significant anti-sickling effectsin vitro as well as in vivo [9]. Angelicin can be found in the fruit of Angelica arcangelica. There is evidence demonstrating that angelicin is a powerful inducer of erythroid differentiation, enhancement of the HbF synthesis in erythroid progenitors and γ-globin mRNA accumulation of human leukemia K562 cells. Red wine, especially the skin of grapes, contains resveratrol which mimics the HbF-inducing activity of HU. Its function in increasing the γ-globin mRNA in human erythroid precursors has been confirmed. Since β-thalassemia cells exhibit a high level of oxidative stress, which eventually shorten the survival of erythroid cells in β-thalassemia patients, resveratrol which exhibits both antioxidant activity and HbF inducing property can become a very promising HbF inducer from the natural world [10].

Conclusion

The study demonstrated the pivotal role of plant-based HbF inducers, based on the investigation of pharmacological agents that can stimulate HbF production. We present HbF-inducing activity-guided isolation of pyrroquinazoline alkaloids from A. vasica in a bioassay-guided manner. Compounds (1) and (2) showed significant reversal of the γ-globin silencing and encouraged the HbF production at lower doses without affecting cellular proliferation, supported by the evident increase in HbF production and γ-globin gene expression in vitro. The in vivo studies underline the therapeutic potential of A. vasica in fetal hemoglobin production at gene and protein levels with protective effects on blood cells and biochemical architectures, which supports the traditional use of A. vasica and would provide a great insight into the therapeutic use of A. vasica and pyrroquinazoline alkaloids in the treatment of hematological diseases.

Chemotherapeutic agents, such as 5-azacytidine, hydroxyurea, myleran, and butyrate, had long been used for β- thalassemia treatment by stimulating HbF synthesis; yet, cytotoxicity, growth-inhibitory effect, fear of long-term carcinogenesis, and only modest HbF-inducing activity have limited the clinical usage of these agents in β-thalassemia and SCD treatment. Also, through understanding the pathology of β-thalassemia, it is revealed that most of the identified HbF-inducing agents have limitation on treating β- thalassemia.

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