Fetal Hemoglobin Inducers in Treatment of β-Hemoglobinopathies

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Review Article

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Evaluation of Novel Fetal Hemoglobin Inducer Drugs in Treatment of β-Hemoglobinopathy Disorders

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ABSTRACT

Objective: The use of fetal hemoglobin (HbF) inducer drugs is considered as a novel approach in treatment of β-hemoglobinopathies, especially β- thalassemia and sickle cell disease. HbF inducers including hydroxyurea, histone deacetylase (HDAC) inhibitor agents such as sodium butyrate, azacitidine, decitabine and new immunomodulator drugs like pomalidomide, lenalidomide and thalidomide can reduce α-globin chain production in erythroid progenitors and improve α: β chain imbalance, the most crucial complication of β-thalassemia.

Materials and Methods: In this article, we reviewed more than 40 articles published from 1979 to 2012 in the field of fetal hemoglobin augmentation.

Results: Recent studies suggest the synergistic effect of drug combinations in efficient induction of fetal hemoglobin and gene over-expression.

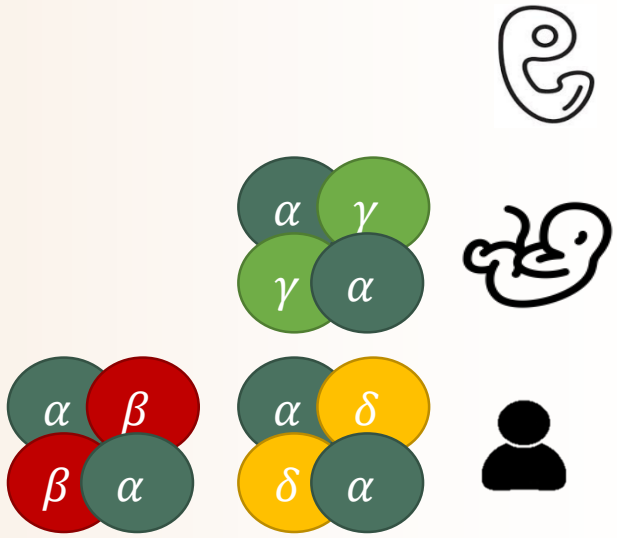
Conclusion: It seems that drugs which act with different molecular and epigenetic mechanisms have proper synergistic effects in fetal hemoglobin induction and gene over-expression.

KEY WORDS: Fetal hemoglobin, β-Hemoglobinopathies, Histone deacetylase

In normal adults, the major Hb is HbA (α2β2), with 2·5–3·5% HbA2 (α2δ2) and, usually, <1% HbF (α2γ2). Interestingly, this residual HbF

Hemoglobin structure

- Embryonic hemoglobin : ε, τ
- Fetal hemoglobin $\alpha_2\gamma_2$
- Adult hemoglobin $\alpha_2\beta_2$
- Adult hemoglobin 2 : $\alpha_2\delta_2$
- Alpha always; gamma goes, becomes beta



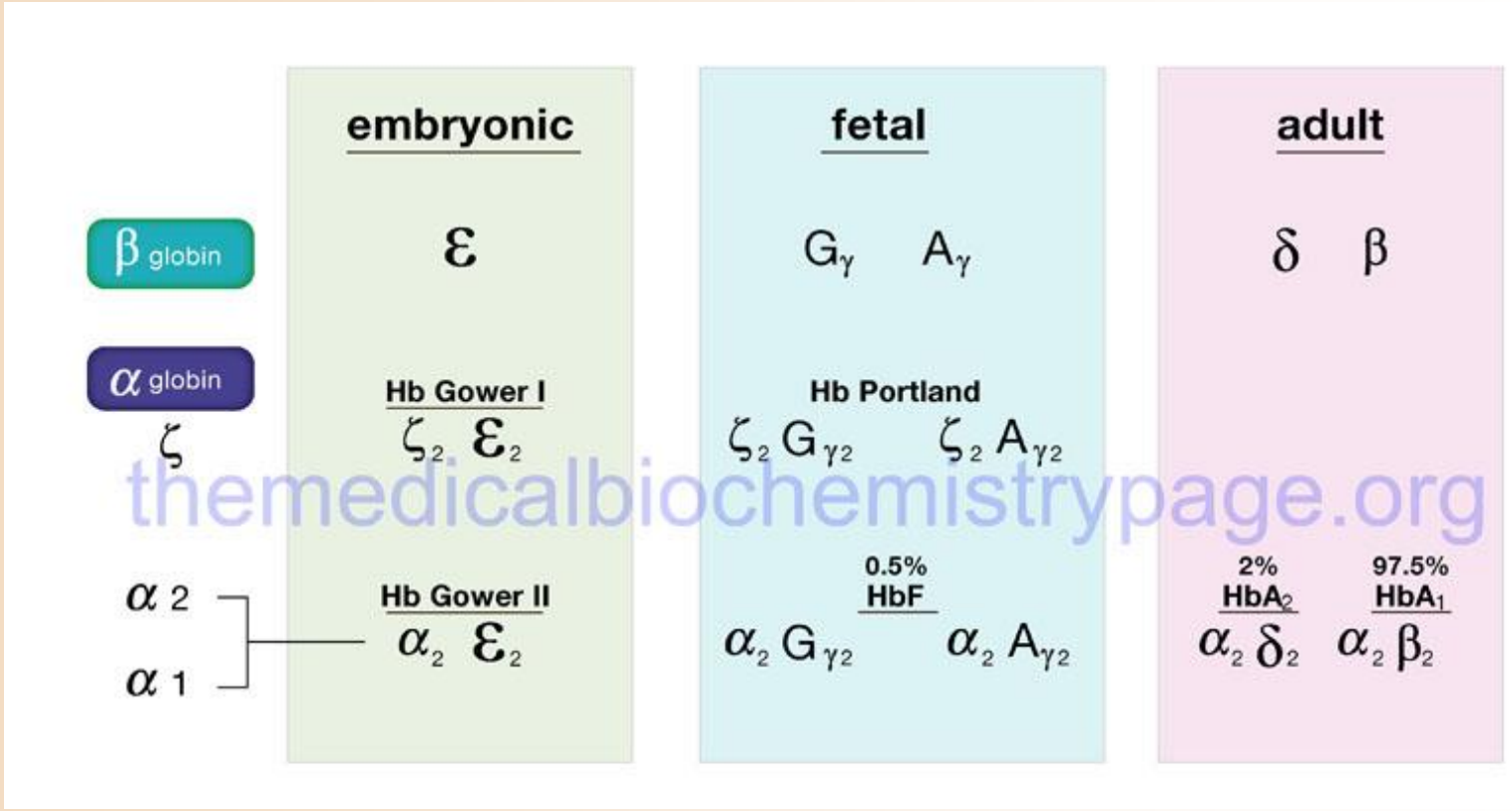
The use of fetal hemoglobin (HbF) inducer drugs is considered as a novel approach in treatment of β-hemoglobinopathies, especially β-thalassemia and sickle cell disease.

HbF inducers including

1-hydroxyurea,

2-histone deacetylase (HDAC) inhibitor agents such as sodium butyrate, azacitidine, decitabine

3- new immunomodulator drugs like pomalidomide, lenalidomide and thalidomide can reduce α-globin chain production in erythroid progenitors and improve α: β chain imbalance, the most crucial complication of βthalassemia.



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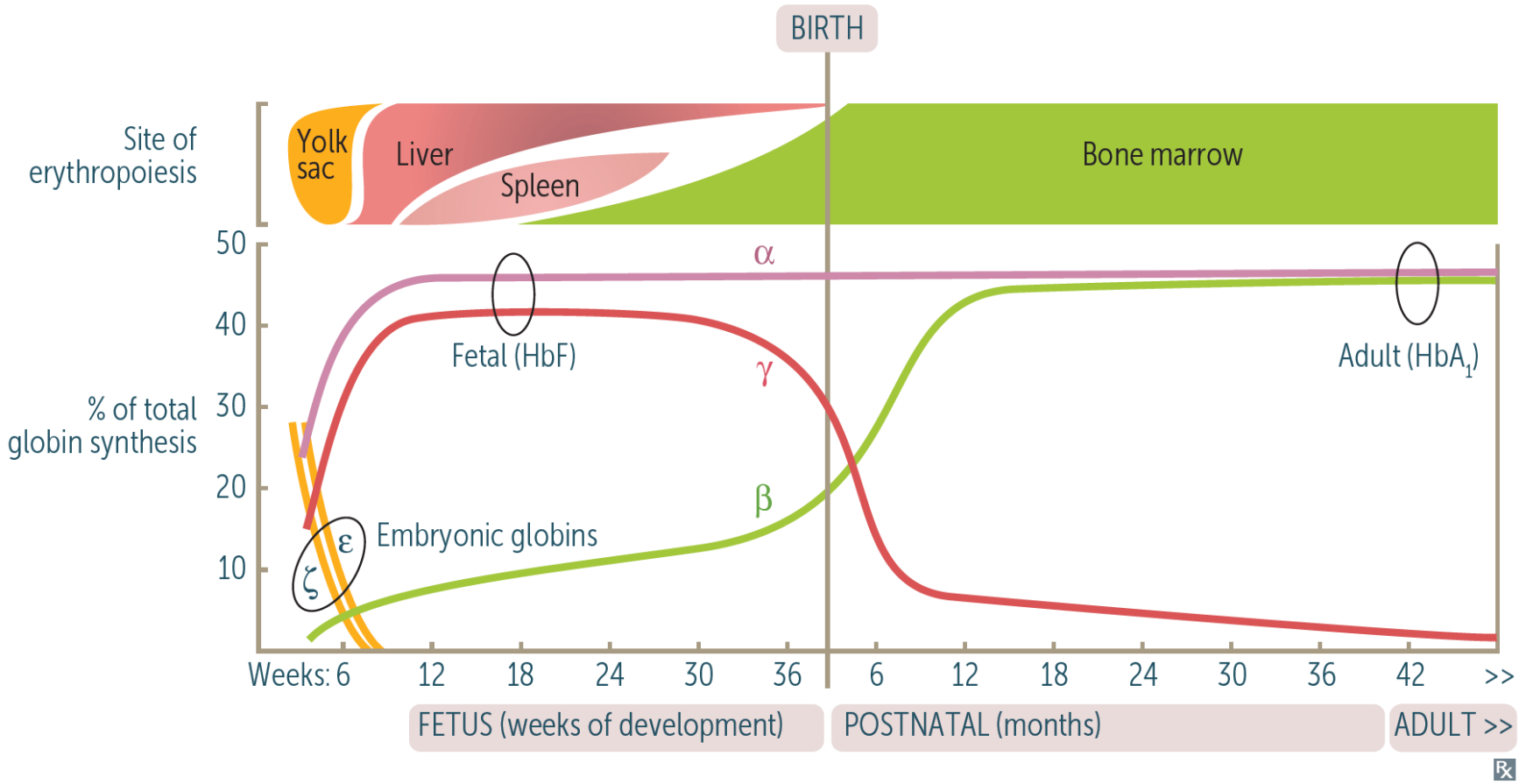
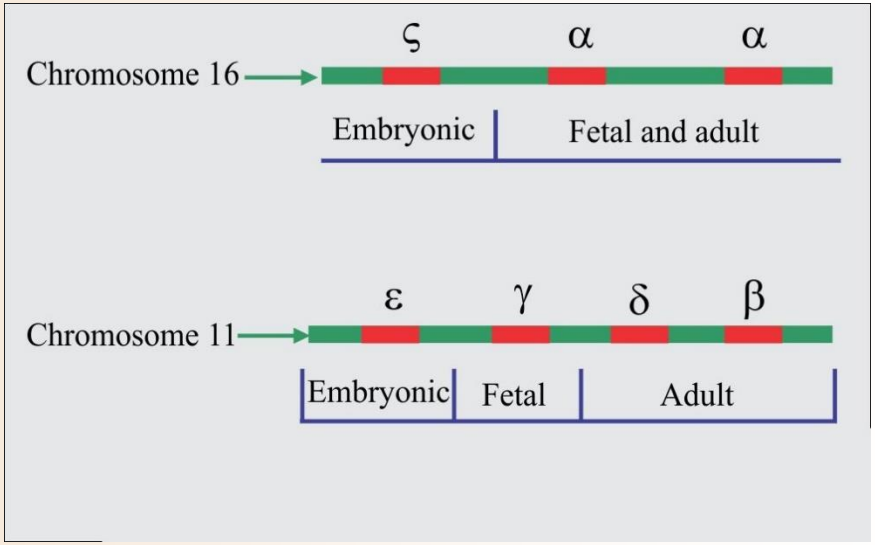
β-globin like gene family is located on chromosome 11, and includes five coding regions from 5' to 3’ comprising ε, γG, γA, δ and β genes, respectively. The placement of genes from 5' to 3’ direction is based on the evolution of gene expression in fetus with predominant expression of ε gene in yolk sac blood islands, γG and γA genes during embryonic period in the liver as well as δ and β genes in the bone marrow in postnatal period. Following switching of γ-globin gene expression to β-globin after birth, complications of β-thalassemia and SCD are manifested. Thus, the use of drugs affecting the silencing of γ-globin gene or preventing it can be regarded as an effective therapeutic approach.


BIRTH
Site of erythropoiesis
Yolk sac
Liver
Spleen
Bone marrow
% of total globin synthesis
50
40
30
20
10
α
γ
β
ε
ζ
Fetal (HbF)
Adult (HbA1)
Embryonic globins
Weeks: 6
12
18
24
30
36
6
12
18
24
30
36
42
>>
FETUS (weeks of development)
POSTNATAL (months)
ADULT >>

THALASSEMIA

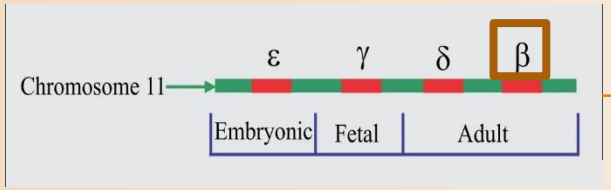
- Alpha thalassemia
  - Gene deletion
  - Cis or trans?
- Beta thalassemia
  - Point mutation and frameshift



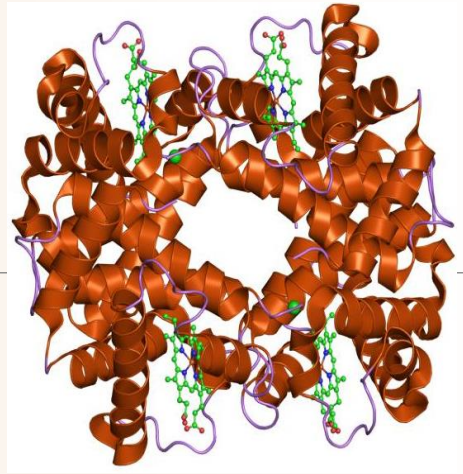
β- hemoglobinopathies

β- thalassemia

Sickle cell



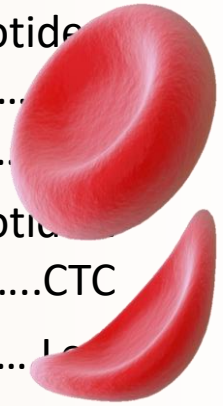
Gene expression



Nucleotide

TCT…. AAG GAG GAG CCT ACT …

Ser…. lys Glu Glu Pro Thr …

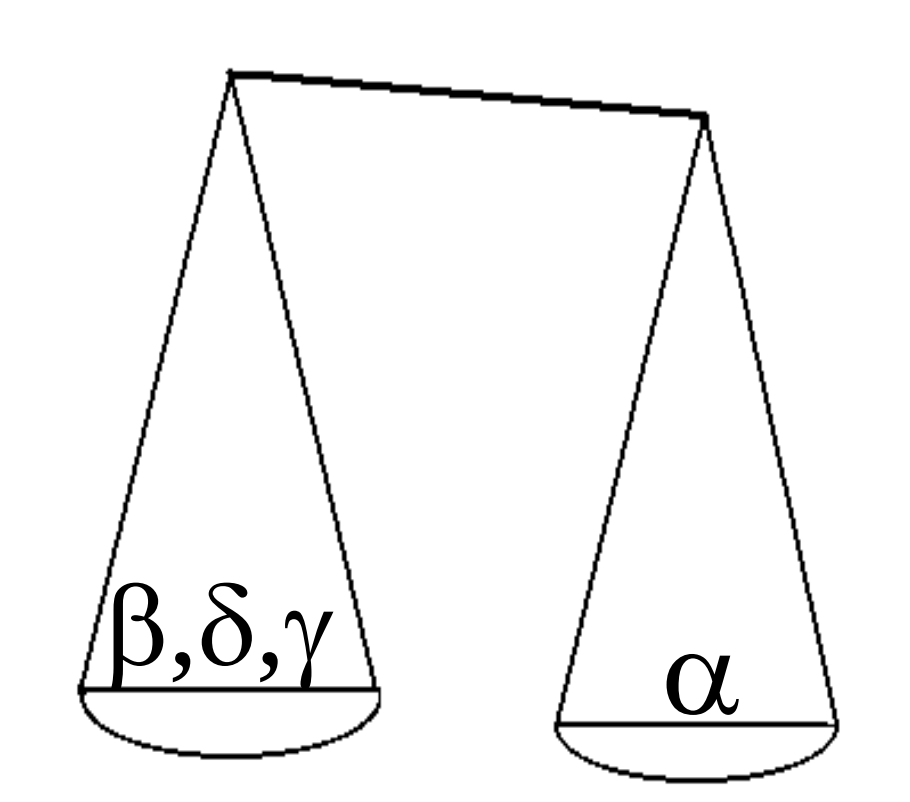


Nucleotide

TCT…. AAG GAG GTG CCT ACT …..CTC

Ser…. lys Glu Val Pro Thr …

In fact, lack of balance between α- globin and β-globin chains is the major factor in the pathology of β- thalassemia



Old fashioned therapy!

Currently, the main focal point of therapy in βthalassemia patients is

1. a regular blood transfusion schedule and
2. use of iron chelating agents.

the only basic therapy: Allogeneic transplantation of hematopoietic stem cell: **donor with compatible HLA can cure patients under 17**

Problems?

finding the donor with compatible HLA

requiring long-term use of immunosuppressive drugs

Epigenetic and expression pattern can be a target for therapy

The change in methylation pattern in DNA level can be therapeutic target:

CpG islands lysine residue acetylation in N-terminal Histone

Medications

1. decrease the methylation in DNA level and increase Histone acetylation in γ- globin gene especially in promoter region
2. induce γ- globin gene expression
3. increase HbF level in patients with β thalassemia and SCD.

A gift called hemoglobin!

HbF expression in βthalassemia → decrease the accumulation and precipitation of α-globin chains → reduces the ineffective erythropoiesis.

HbF is not the full blooded hemoglobin

But!

Reduces the clinical morbidity and mortality in patients with βthalassemia and SCD

Fetal Hemoglobin Gene Inducing Agents

Hydroxyurea (HU) is considered as an inducer of HbF production:

reduces the number of white blood cells and prevents their activation inhibits vascular occlusion in e patients.

Disappointment

The effect of HU in treating patients with β-thalassemia major and intermedia has been very disappointing why?

requirement for much more HbF to achieve globin chain balance in this disease and to the inability to escalate hydroxyurea dosing as a result of cytopenias and it has not made any significant improvement in the anemia either.

In fact, this drug results in regeneration of erythroid series through its cytotoxic effects, and releases nitric oxide (NO) through metabolic effects.

The NO induced HbF via recruitment of P38 Mitogen-activated protein kinase (p38 MAPK) pathway.

Histone deacetylase (HDAC) inhibitors

- butyrate derivatives
- Azacitidine
- decitabine (5-aza 2-deoxycytidine)
- trichostatin-A

Change the epigenetic patterns of β-globin cluster such as increasing histone H3 acetylation and decreasing methylation in γ- globin gene promoter.

Azacitidine is considered an inducer drug with a high potential to increase production of fetal hemoglobin. Azacitidine and decitabine act as HDAC and DNA methyl transferase (DNMT) inhibitors that result in increased HbF.22-27 Decitabine, the analogous drug of azacitidine, has a higher potential in DNMT enzyme inhibition compared with azacytidine, as well as in activation of tumor suppressor genes.

This drug has had proper therapeutic effects in patients with sickle cell anemia, even in patients resistant to HU.

HU has the potential of γ-globin gene induction as well as reduction of the expression of β- globin gene and has anti-sickling effects, but it is effective in approximately 50% of SCD, and is less effective in increasing HbF for β-thalassemia patients.

butyrate derivative

- sodium butyrate
- arginine butyrate

low risk and highly effective in treatment of sickle cell anemia and thalassemia.

Continuous or intermittent

The studies have shown that the level of HbF is increased by the same rate following intermittent and continuous administration of butyrate.

Butyrate is somehow solution

induce γ-gene expression

Increase the expression of β-globin gene, while azacitidine has no effect on β-globin gene expression.

increase histone acetylation in ε gene, but there is no increase in expression of ε gene following this phenomenon. This is due to other factors such as specific transcription factors and epigenetic changes in LCR.

hemin

has a similar function as butyrate in changing the pattern of gene expression but in a lower extent.

This compound is an inducer of erythropoiesis with contradictory effects on α- globin gene expression

these two compounds increase the level of α- globin gene mRNA in β-thalassemia patients while reducing its level in SCD patients.

Nicotinic acid

HbF inducers

1. stimulate erythroid differentiation in K562 cell line
2. reduce glycophorin A (GphA) expression

Pomalidomide

acetylation of H3K9 and H3K14 at LCR region of γglobin gene.

- this epigenetic pattern is locus specific without any global changes in H3 acetylation pattern.

synergistic effect with HU in the induction of HbF.

In this drug family, thalidomide used for multiple myeloma treatment has appropriate effects in HbF induction with similar mechanism of action with other immunomodulatory agents.

The exact mechanism of the therapeutic effect of this factor is still unknown.

Thalidomide and teratogen

the effects of thalidomide may be due to suppression of NF-KB induction by inflammatory cytokines such as Tumor Necrosis Factor (TNF- α), Vascular Endothelial Growth Factor (VEGF) and prostaglandin E2 synthesis (PG-E2) associated with increased release of reactive oxygen species (ROS). ROS can launch P38 MAPK, which results in increased HbF levels but has teratogenic effects.

recent studies indicate a synergistic effect of different concentrations of sodium butyrate and thalidomide in induction of β- and γ-globin genes in erythroid cells derived from CD133+ cells in cord blood. Other findings also indicate a high potential of this drug combination in inducing the production of erythroid precursors compared with single-drug treatments. Comparison of the effects of sodium butyrate and thalidomide in gene expression induction suggests higher capacity of the latter in increasing production of β- and γ-globin genes

In other studies, cytokines like stem cell factor (SCF) and transforming growth factor-beta (TGF-β) have been shown to have HbF induction potential. It is seen that MAPK signaling pathway is associated with fetal hemoglobin induction using SCF. This signaling pathway affects the regulatory region in βglobin gene cluster through increased expression of NF-E2 transcription factor. TGF-β also induces the expression of this gene through activation of fetal Krüppel-like transcription factor (FKLF) through recognition of its direct effect in γ-globin gene expression. Another study reports the synergistic effect of SCF, TGF-β and erythropoietin (EPO) in fetal hemoglobin expression induction in erythroid progenitor cells in vitro.

DNMT inhibitors such as azacitidine and decitabine are potent HbF inducers and are used in SCD patients ***resistant to HU***.

These drugs are useful for patient with severe SCD and β-thalassemia. DNMTs have been administered to these patients with good results, but their use is limited because of concerns about potential carcinogenic effects.

All these HbF inducers have mutagenic and carcinogenic effects and cause clinical toxicity, among which only HU has been useful for long term clinical treatment. In a prospective view, recent studies suggest new approaches for HbF induction such as targeting BCL11A and ELKF (transcription factors involved in Hb switching). Other researches focus on miRNAs (for example, miR that targets α-globin to prevent its precipitation) as therapeutic goals with less side effects.

Targeted Therapeutic Strategies for Fetal Hemoglobin Induction

Vijay G. Sankaran[1-3]

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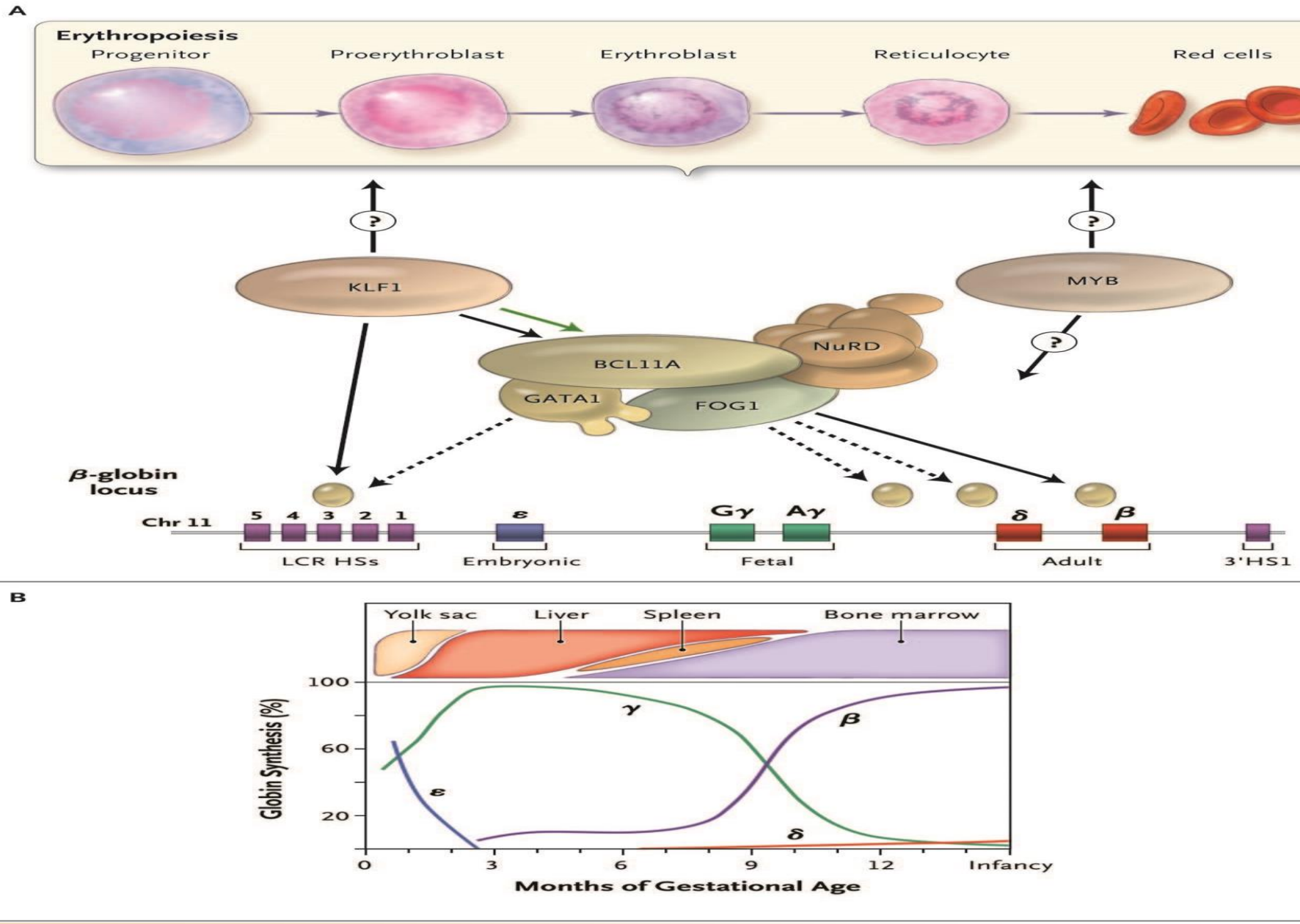
Increased levels of fetal hemoglobin (HbF) can ameliorate the severity of the β-hemoglobin disorders, sickle cell disease (SCD) and β-thalassemia, which are major sources of morbidity and mortality worldwide. As a result, there has been a longstanding interest in developing therapeutic approaches for inducing HbF. For more than 3 decades, the majority of HbF inducers developed were based on empiric observations and have had limited success. Recently, human genetic approaches have provided insight into previously unappreciated regulators of the fetal-to-adult hemoglobin switch and HbF silencing, revealing molecular targets to induce HbF. This article reviews these developments and discusses how molecules including BCL11A, KLF1, MYB, SOX6, miRNAs 15a and 16-1, and histone deacetylase 1 and 2 (HDAC1/2) could be important targets for HbF induction in humans. The current understanding of how these molecules function and the benefits and drawbacks of each of these potential therapeutic targets are also


A
Erythropoiesis
Progenitor
Proerythroblast
Erythroblast
Reticulocyte
Red cells
?
KLF1
?
MYB
BCL11A
NuRD
GATA1
FOG1
?
β-globin locus
Chr 11
5 4 3 2 1
ε
Gγ
Aγ
δ
β
LCR HSs
Embryonic
Fetal
Adult
3'HS1
B
Yolk sac
Liver
Spleen
Bone marrow
Globin Synthesis (%)
100
60
20
γ
β
ε
δ
0
3
6
9
12
Infancy
Months of Gestational Age

Original Article

Synergistic Effect of Simvastatin and Romidepsin on Gamma-globin Gene Induction

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Abstract

Objective: Hemoglobinopathies such as beta-thalassemia and sickle cell disease (SCD) are inherited disorders that are caused by mutations in beta-globin chain. Gamma-globin gene reactivation can ameliorate clinical manifestations of beta-thalassemia and SCD. Drugs that induce fetal hemoglobin *(HbF)* can be promising tools for treatment of beta-thalassemia and SCD patients. Recently, it has been shown that Simvastatin (SIM) and Romidepsin (ROM) induce HbF. SIM is a *BCL11a* inhibitor and ROM is a *HDAC* inhibitor and both of these drugs are Food and Drug Administration (FDA)-approved for hypercholesterolemia and cutaneous T-cell lymphoma respectively. Our aim was to evaluate the synergistic effects of these drugs in inducing HbF.

Materials and Methods: In our experimental study we isolated CD34+ cells from five cord blood samples that were cultured

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Trienone analogs of curcuminoids induce fetal hemoglobin synthesis via demethylation at $^{G}\gamma$-globin gene promoter

Khanita Nuamsee[1,2,3], Thipphawan Chuprajob[4,5], Wachirachai Pabuprapap[4], Pornrutsami Jintaridth[6], Thongperm Munkongdee[2], Phatchariya Phannasil[2], Jim Vadolas[7,8], Pornthip Chaichompoo[3], Apichart Suksamrarn[4] & Saovaros Svasti[2,9]✉

The reactivation of γ-globin chain synthesis to combine with excess free α-globin chains and form fetal hemoglobin (HbF) is an important alternative treatment for β-thalassemia. We had reported HbF induction property of natural curcuminoids, curcumin (Cur), demethoxycurcumin (DMC) and *bis*-demethoxycurcumin (BDMC), in erythroid progenitors. Herein, the HbF induction property of trienone analogs of the three curcuminoids in erythroleukemic K562 cell lines and primary human erythroid progenitor cells from β-thalassemia/HbE patients was examined. All three trienone analogs could induce HbF synthesis. The most potent HbF inducer in K562 cells was trienone analog of BDMC (T-BDMC) with 2.4 ± 0.2 fold increase. In addition, DNA methylation at CpG −53, −50 and +6 of $^{G}\gamma$-globin gene promoter in K562 cells treated with the compounds including T-BDMC (9.3 ± 1.7%, 7.3 ± 1.7% and 5.3 ± 0.5%, respectively) was significantly lower than those obtained from the control cells (30.7 ± 3.8%, 25.0 ± 2.9% and 7.7 ± 0.9%, respectively $P < 0.05$). The trienone compounds also significantly induced HbF synthesis in β-thalassemia/HbE erythroid progenitor cells with significantly reduction in DNA methylation at CpG +6 of $^{G}\gamma$-globin gene promoter. These results suggested that the curcuminoids and their three trienone analogs induced HbF synthesis by decreased DNA methylation at $^{G}\gamma$-globin promoter region, without effect on $^{A}\gamma$-globin promoter region.

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Article

Discovery of Novel Fetal Hemoglobin Inducers through Small Chemical Library Screening

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Abstract: The screening of chemical libraries based on cellular biosensors is a useful approach to identify new hits for novel therapeutic targets involved in rare genetic pathologies, such as β-thalassemia and sickle cell disease. In particular, pharmacologically mediated stimulation of human γ-globin gene expression, and increase of fetal hemoglobin (HbF) production, have been suggested as potential therapeutic strategies for these hemoglobinopathies. In this article, we screened a small chemical library, constituted of 150 compounds, using the cellular biosensor K562.GR, carrying enhanced green fluorescence protein (EGFP) and red fluorescence protein (RFP) genes under the control of the human γ-globin and β-globin gene promoters, respectively. Then the identified compounds were analyzed as HbF inducers on primary cell cultures, obtained from β-thalassemia patients, confirming their activity as HbF inducers, and suggesting these molecules as lead compounds for further chemical and biological investigations.

Keywords: hemoglobinopathies; β-thalassemia; sickle cell disease; fetal hemoglobin; chemical screening; compound library; cellular biosensors

Epigenetic Reexpression of Hemoglobin F Using Reversible LSD1 Inhibitors: Potential Therapies for Sickle Cell Disease

Steven Holshouser, Rebecca Cafiero, Mayra Robinson, Joy Kirkpatrick, Robert A. Casero, Jr., Hyacinth I. Hyacinth, and Patrick M. Woster*

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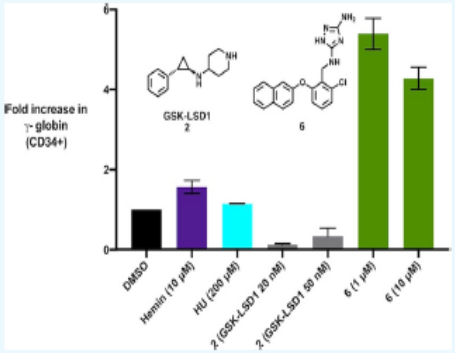
ABSTRACT: Sickle cell disease (SCD) is caused by a single nucleotide polymorphism on chromosome 11 in the β-globin gene. The resulting mutant hemoglobin S (HbS) is a poor oxygen transporter and causes a variety of vascular symptoms and organ failures. At birth, the DRED epigenetic complex forms and silences the γ-globin gene, and fetal hemoglobin (HbF, 2 α-, and 2 γ-subunits) is replaced by adult HbA ($\alpha_2\beta_2$) or HbS ($\alpha_2\beta^s{}_2$) in SCD patients. HbF is a potent inhibitor of HbS polymerization, thus alleviating the symptoms of SCD. The current therapy, hydroxyurea (HU), increases γ-globin and the HbF content in sickle cells but is highly underutilized due to concern for adverse effects and other complications. The DRED complex contains the epigenetic eraser lysine-specific demethylase 1 (LSD1), which appears to serve as a scaffolding protein. Our recently discovered 1,2,4-triazole derivatives and cyclic peptide LSD1 inhibitors promote the upregulation of γ-globin production in vitro without significant toxicity. Herein, we demonstrate that these LSD1 inhibitors can be used to disrupt the DRED complex and increase the cellular HbF content in vitro and in vivo. This approach could lead to an innovative and effective treatment for SCD.



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PAPER

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Cinchona alkaloids as natural fetal hemoglobin inducing agents in human erythroleukemia cells

Fizza Iftikhar, [a] Hamad Ali [a] and Syed Ghulam Musharraf *[ab]

Pharmacologically mediated reactivation of γ-globin gene with an increase in fetal hemoglobin production, is a cost effective experimental therapeutic intervention for the management of β-hemoglobinopathies. Investigation of new pharmacological agents as HbF inducers from natural resources is desirable to develop safe and effective HbF inducers. We evaluated selected cinchona alkaloids (cinchonidine and quinidine) for their potential of erythroid differentiation and augmentation of fetal hemoglobin production. K562 cells were used as *in vitro* experimental model. Erythroid differentiation of K562 cells was studied using a benzidine assay, and total hemoglobin was estimated through a calorimetric method. Whereas, quantitative real-time PCR (qRT-PCR) was used to analyse γ-globin gene expression, and flow cytometry and immunofluorescence microscopy for evaluating HbF production. Cinchona alkaloids showed dose dependent erythroid differentiation, time driven cellular proliferation, with kinetics of hemoglobin accumulation in K562 cells. The findings of qRT-PCR showed an increase in expression of γ-globin mRNA content (3.17-fold in cinchonidine and 2.03-fold increase in quinidine treated K562 cells), accompanied by an increase in fetal hemoglobin production. Altogether, this study demonstrates that cinchona alkaloids can be used as therapeutic agents in treating β-thalassemia after further biological investigation.

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Review Article

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Piceatannol: A Potential Futuristic Natural Stilbene as Fetal Haemoglobin Inducer

Haematology Section

AAYUSH KUKREJA[1], SAMARTH TANDON[2], AMIT MISHRA[3], ARCHANA TIWARI[4]

ABSTRACT

Beta thalassaemia is an autosomal recessive inherited blood disorder which results in abnormal formation of Haemoglobin molecule and ineffective erythropoiesis. Patients need to be dependent on habitual blood transfusion and on unaffordable exorbitant therapies for continued existence. It has been hypothesized that if the level of foetal Haemoglobin increases, it compensates the need of adult Haemoglobin and hence, ameliorates clinical symptoms associated with beta thalassaemia major. Illation from previous studies has proved that reactivation of foetal Haemoglobin with the aid of natural compounds is a better alternative therapy for patients of beta thalassaemia because of its cost effectiveness and occurrence in natural eatables. Piceatannol, a naturally occurring stilbene, is less studied compound in comparison to resveratrol, but it shows a wide range of biological activities. This article has mainly focused on piceatannol and its application as a foetal Haemoglobin inducer in future.

INVITED REVIEW ARTICLE

Genome editing strategies for fetal hemoglobin induction in beta-hemoglobinopathies

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Abstract

Genome editing to correct a defective β-globin gene or induce fetal globin (HbF) for patients with beta-hemoglobinopathies has the potential to be a curative strategy available to all. HbF reactivation has long been an area of intense interest given the HbF inhibition of sickle hemoglobin (HbS) polymerization. Patients with HbS who also have high HbF tend to have less severe or even minimal clinical manifestations. Approaches to genetically engineer high HbF include *de novo* generation of naturally occurring hereditary persistence of fetal hemoglobin (HPFH) mutations, editing of transcriptional HbF repressors or their binding sites and/or regulating epigenetic intermediates controlling HbF expression. Recent preclinical and early clinical trial data show encouraging results; however, long-term follow-up is lacking, and the safety and efficacy concerns of genome editing remain.

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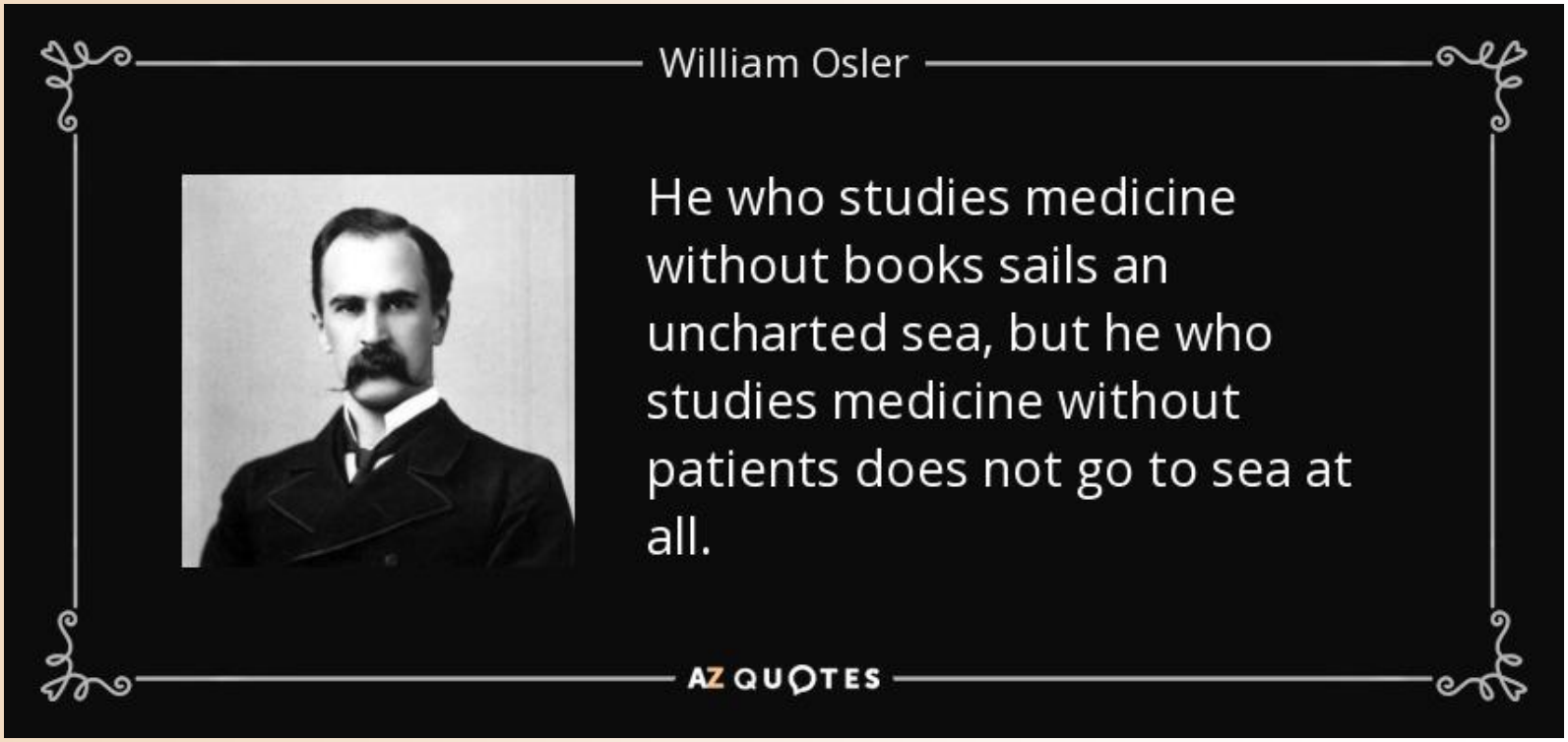
Abstract

Genome editing to correct a defective β-globin gene or induce fetal globin (HbF) for patients with beta-hemoglobinopathies has the potential to be a curative strategy available to all. HbF reactivation has long been an area of intense interest given the HbF inhibition of sickle hemoglobin (HbS) polymerization. Patients with HbS who also have high HbF tend to have less severe or even minimal clinical manifestations. Approaches to genetically engineer high HbF include *de novo* generation of naturally occurring hereditary persistence of fetal hemoglobin (HPFH) mutations, editing of transcriptional HbF repressors or their binding sites and/or regulating epigenetic intermediates controlling HbF expression. Recent preclinical and early clinical trial data show encouraging results; however, long-term follow-up is lacking, and the safety and efficacy concerns of genome editing remain.

The father


William Osler
He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.
AZ QUOTES