

Epigenetic Modulations on the Fetal Hemoglobin Induction

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In recent years of experience fetal hemoglobin (HbF) induction considers as novel therapeutic approach for β -thalassemia and sickle cell in therapeutic approaches. Several pharmacologic agents such as Hydroxyurea, Azacytidine, butyrate derivatives and immunomodulator drugs like Pomalidomide and Lenalidomide could be able to up-regulate HbF level with different molecular and epigenetic patterns.(1- 4) The epigenetic modifications including DNA methylation and histone modification play an important role in γ -globin gene over-expression in mature stage of erythropoiesis. Butyrate and Azacytidine consider as well-known histone deacetylase (HDAC) inhibitor and DNA methyltransferase-1 (DNMT-1) inhibitor. These agents reversed the switching of β -globin gene to γ -globin gene with decreasing of DNA methylation in CpG islands of β -like globin genes promoter. Also, these two agents increase histone H3 and H4 acetylation at the promoter of β -globin cluster. These epigenetic changes result in the efficient up-regulation of γ -globin gene at different developmental stages of erythropoiesis.(5, 6) Thalidomide could be able to increase H4 acetylation via activation of p38 in MAPK pathway for its HbF induction.(7) Other studies show the potential role of Pomalidomide in γ -globin gene induction with increasing of acetylation of histone H3 lysines 9 and 14 (H3K9 & H3K14) at the promoters of human β -globin genes.(8)

Recently, we studied the *in vitro* effects of single and combination treatments of Thalidomide and Sodium butyrate on the methylation of histone H3K27 as heterochromatin mark at the promoter of β -globin cluster. We showed that Thalidomide much effective in suppression of H3K27 methylation in comparison with Sodium butyrate. Besides, Thalidomide has more potential to decrease H3K27 methylation than combination treatment of Thalidomide and Sodium butyrate, regarding to the synergistic effect of combination treatment on γ -globin gene induction compared to single treatments.(9- 11) These data suggest that combination treatment of Thalidomide and Sodium butyrate could play a critical role on γ -globin gene induction with different epigenetic models.

In conclusion, we suggest further investigation on epigenetic mechanisms of γ -globin gene induction for elucidation of the molecular mechanisms of gene induction.

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