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**Title: HEXIM1 AND GATA1 COOPERATE TO REGULATE ERYTHROID GENE EXPRESSION AND FUNCTION**

**Abstract**

During steady state erythropoiesis, new erythrocytes are generated at a constant state but upon anemic stress, erythroid output is greatly increased. For erythroid progenitors to mature into erythrocytes, they continuously accumulate hemoglobin and transcriptionally silence non-erythroid genes. Previous work in our lab shows that such changes in gene expression are associated with a dramatic decline in histone marks associated with active transcription elongation (Murphy Blood 2021). HEXIM1 is a key regulator of RNA Polymerase II (Pol II) activity and our functional studies demonstrated a pro-proliferation role of HEXIM1 during erythropoiesis. We saw a drastic increase of gamma globin production and decrease of beta globin upon HEXIM1 overexpression (OE), along with upregulation of a group of fetal factors that promote the expression of gamma-globin. These changes are similar to what is observed during stress erythropoiesis. Genome wide profiling of Pol II and GATA1 following HEXIM1 OE suggests that HEXIM1 promotes the pioneer activity of GATA1 at fetal genes and thereby selectively regulates transcription. Together, our data suggest that HEXIM1 promotes erythroid proliferation and a fetal phenotype by working with GATA1 to activate a specific transcriptional program, and have potentially identified novel therapeutic targets for blood disorders that benefit from induction of HbF production, such as sickle cell disease and  $\beta$ -thalassemia. These data are also likely to provide insights into the mechanisms that regulate the response to anemic stress.