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CORRELATION BETWEEN ZINC AND HEMOGLOBIN F

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Establishing a Link between Zinc Homeostasis and Globin Gene Expression.

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Sickle cell disease (SCD) affects millions of people around the world and is the most common inherited disease in the United States, affecting 1 of 1800 births and 1 of 400 African-American births. Patients with SCD have an improved clinical course when fetal hemoglobin (HbF) levels are increased, and this is the basis for treatment with hydroxyurea as a disease modifying therapy. Hydroxyurea has been shown to decrease the frequency of pain episodes and decrease the incidence of stroke in patients who are at risk based on transcranial doppler velocities. Hydroxyurea is one of two FDA approved treatments for SCD patients, so there is need for new therapies, including the identification of druggable transcriptional activators that specifically up-regulate the gamma-globin genes (HbF). Understanding the mechanisms underlying control of globin gene expression, particularly those involved in activation of gamma-globin gene expression, is important for developing new treatments for SCD.

Metal-responsive transcription factor-1 (MTF-1) is a key regulator of zinc metabolism in higher eukaryotes that controls the metal-inducible expression of metallothioneins and a number of other genes directly involved in the intracellular sequestration and efflux transport of zinc. Bao et al published that adults with SCD showed increased red blood cells (RBCs), hemoglobin (Hb) and hematocrit levels after 3 months of zinc supplementation compared to the placebo group. Furthermore, previous studies demonstrated that MTF-1 plays an essential role in liver development and that MTF-1-deficient mice display an anemic phenotype, suggesting a role for MTF-1 in hematopoiesis. In our study, we observed a 2.4-fold increase in gamma-globin expression in K562 cells at 4 hours. We also demonstrated increased gamma-globin expression in adult blood from MTF-1 overexpression, human beta-globin locus yeast artificial chromosome (beta-YAC) bi-transgenic (bigenic) mouse lines at the mRNA level by quantitative real-time RT-PCR (qPCR) and at the protein level by FACS analysis. Lastly, gamma-globin gene expression was induced 12-fold in bone marrow cells (BMCs) derived from these bigenic mice compared to BMCs derived from beta-YAC-only mice, and 3-fold after 6 hours of zinc treatment in beta-YAC-only BMCs.

Co-immunoprecipitation (Co-IP) analysis showed that GATA-2 associated with MTF-1 in MTF-1 overexpression, beta-YAC BMCs, but not in beta-YAC-only BMCs, suggesting that reactivation of gamma-globin expression by MTF-1 might be mediated by a MTF-1-GATA-2 protein complex. Chromatin immunoprecipitation (ChIP) experiments indicated that MTF-1 and GATA-2 co-occupy the same sites in the gamma-globin promoter. Our data suggest that activation of gamma globin by MTF-1 is mediated by protein-protein interaction with GATA-2 and that this multi-protein complex is targeted to GATA sites located in the gamma-globin gene-promoters via binding of the GATA-2 protein.

Based on our data, we hypothesize that zinc supplementation will increase plasma HbF by inducing MTF-1 thus activating gamma-globin gene expression. This protein represents a potential new target in strategies to reactivate gamma-globin in hemoglobinopathies where higher levels of HbF would have beneficial effects. More clinical and basic science studies are

needed to further characterize the role of zinc in globin gene expression and hemoglobin F levels in the clinical setting.