β-Thalassemias are a group of inherited blood disorders caused by loss of β-globin synthesis and are characterized by anemia, extramedullary hematopoiesis and ineffective erythropoiesis leading to secondary iron overload. Increased iron absorption due to inadequate synthesis of the hormone hepcidin (HAMP). The membrane serine protease Matrilysin-1 (TMPRSS5) interacts with BMP6/9 promoter to elevate hepcidin expression and reduce disease severity in the β-thal/mice. TMPRSS5 knockdown (β-thal/∆) decreases hepcidin expression and increases serum iron concentration. This study demonstrates the efficacy of this therapeutic approach, that BMP6/9 animals were treated with an siRNA directed against Tmprss10 on a replete 50ppm iron diet, a low iron diet or a 50ppm iron diet containing deferiprone. Administration of Tmprss1 siRNA in all conditions leads to elevation of Tmprss1 mRNA in the livers of β-thal/mice with concomitant elevation in hepcidin expression. In correspondence with earlier studies, we demonstrate here that Tmprss1 silencingparallel each of the three diet regimens leads to an improvement in the anemia of β-thal/mice as evidenced by increased total hemoglobin. Furthermore, hallmarks of ineffective erythropoiesis, including splenomegaly and reticulocytosis, were decreased in all Tmprss1 silenced β-thal animals. If untreated, excessive iron loading in humans with β-thalassemia leads to tissue iron deposition and eventual organ damage and failure. Importantly, here we demonstrate that the total body iron burden of β-thal/mice, as assessed by non-invasive MRI, is decreased by almost 30% in animals treated with both oral deferiprone and Tmprss1 siRNA. A similar diminution of iron deposition is not evident in animals on low iron diet or in mice fed deferiprone alone. Together, this data suggest that siRNA suppression of Tmprss1, in conjunction with therapeutic intervention, may provide an improved modality for treatment of the anemia and secondary iron loading seen in hemoglobinopathies such as β-Thalassemia.

Conclusions

• Tmprss1 silencing animals under three diet regimens leads to improvement in the anemia of Hbb6.1+/− mice and ameliorates hallmark of ineffective erythropoiesis, including splenomegaly and elevated reticulocytes.

• Importantly, we demonstrate that the total body iron burden of thalassemic mice is decreased by almost 30% in animals chelated with oral deferiprone and treated with Tmprss1 siRNA.

• This data suggest that siRNA suppression of Tmprss1, in conjunction with chelation therapy, may provide an improved modality for treatment of the anemia and secondary iron loading seen in hemoglobinopathies such as β-Thalassemia.

References


Figure 1. Tmprss1 is a negative regulator of hepcidin expression

Hepcidin expression is increased in response to elevated iron and decreased due to ineffective erythropoiesis, such as is found in β-thalassemia intermedia. Mutations in hemoglobin (HbV) cause hereditary hemolytic anemia. HbV is a monocytic hepcidin protein (BMP) co-receptor, plays a central role in iron homeostasis. BMP4 is transduced through a SMAD signaling cascade. BMP4 expression increases due to BMP4 and BMP receptor conditions and acts as a ligand, binding to HJV and initiating hepcidin expression. The membrane-bound serine protease TMPRSS5 cleaves HJV from the cell surface, forming a soluble protein (sHJV).