

SP5: Thalassemia and iron deficiency anemia: Jane-Jane Chen, Ph.D. (Institute of Medical Engineering & Science, MIT)

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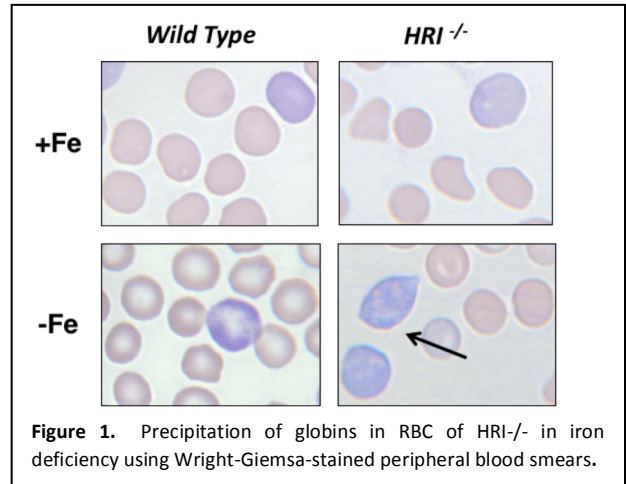
Associated With: TRD2

Significance: Anemia, caused by iron deficiency and thalassemia, is the single most prevalent disorder worldwide. Just iron deficiency anemia has a staggering rate of more than 30% and accounts for approximately 2 billion cases (1). Likewise, thalassemia – the most common monogenic disease that limits the capability of affected hemoglobin to transport oxygen, accounts for ~5% of world's population carrying this trait. Increased oxidative stress and ineffective erythropoiesis in thalassemia may result in the major clinical manifestation of these chronic diseases, including slowed growth in children (2, 3), bone deformities (4), and enlarged spleen, liver, or heart (5, 6). In most cases of anemia, low immunity of individuals may lead morbidity from infections at all ages. While iron deficiency anemia can be treated with proper diet and iron supplements, mild to severe thalassemia is typically managed through blood transfusions and iron chelation therapy. In some cases, surgical interventions (e.g., splenectomy) may be needed to ensure optimal control of associated morbidity (7).

Dr. Chen's laboratory is among the leading groups in the translational regulation involving eIF2 α kinases (8-17). Phosphorylation of eIF2 α is an ancient and conserved mechanism for stress adaptation from yeast to human. The heme-regulated eIF2 α kinase (HRI) is essential for the adaptation of iron-deficiency anemia (13). HRI is a heme-regulated protein kinase that phosphorylates the α -subunit of eIF2, impairing another round of translational initiation and thereby inhibiting translation. During iron/heme deficiency, HRI is necessary to coordinate translation of α - and β - globin mRNAs with the availability of heme for the adaptation to oxidative stress and for reducing ineffective erythropoiesis. In HRI deficiency, excess globins synthesize precipitates and cause proteotoxicity. Besides heme deficiency, HRI is also activated by oxidative stress and denatured proteins (10) both of which occur in thalassemia (11). Furthermore, HRI is necessary for reducing the phenotypic severities of β -thalassemia in mice (11). In addition to understanding the molecular basis of erythroid cell adaptation to oxidative stress, Dr. Chen's Lab is also investigating genome-wide *in vivo* translational regulation during normal and stress erythropoiesis.

Approach: The deformability of red blood cells is known to be reduced in thalassemia as well as in iron deficiency anemia (18, 19). Quantitative assessment of the biomechanical and morphological changes red cells go through during different pathophysiological stages of thalassemia can provide great insight into the disease mechanism complementary to genomic and biological studies. Most existing methods to study cell biomechanics include atomic force microscopy (AFM) (20), optical and magnetic tweezers (21, 22), and pipette aspiration (23-25) are invasive and low throughput. In this context, the optical methods developed at the LBRC (26, 27) have proven to be extremely useful in studying red cell biomechanics (28, 29), particularly during malaria infection (30) and different morphological changes (31). We will transport blood samples derived from iron deficient HRI $-/-$ and eAA (erythroid specific knockin mouse defective in the phosphorylation of eIF2 α) mice from Chen's laboratory to the LBRC facilities for high throughput single cell as well as population level cell biomechanical studies.

Center Offering: LBRC houses state-of-the-art interferometric instruments, quantitative phase microscopy (26, 27), for measuring nanometer scale cell membrane fluctuations and hence quantitative assessment of red cell biomechanical properties at single cell level. The LBRC also houses tomographic phase microscopy (32, 33) units for corresponding 3D morphological measurements as well as cell dry mass, Hb concentration, and total Hb volume. For population level studies, LBRC is able to offer an automated microfabricated 'deformability cytometer' (developed by Dr. Ming Dao's Lab) capable of high throughput (10^3 – 10^4 individual red cells) in a population (34). Altogether, these technologies will provide a unique opportunity for Dr. Chen's Lab to study biophysical aspects of red cells from murine models of iron deficiency anemia while simultaneously investigating the molecular and genomic aspects of various heme-regulated protein kinases in these anemic diseases.



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