TMPRSS6 Mutants, Ninja Turtles, and Anemia

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Faculty Discussant, Dr. Greg del Zoppo
CC:ID 17 year old woman with history of chronic anemia, documented at approximately age 6, who presents for care.

HPI
• Patient indicates that she has been anemic as long as she remembers.
• After an extensive work-up, including bone marrow examination, was unrevealing, patient was started on oral iron replacement.
• Unfortunately, the treatment was without benefit and patient received periodic blood transfusions.
History

PMH
• Chronic anemia

Meds
• None

Social History/Family History
• Recently moved to Seattle; adopted at age 2

ROS
• Minimal fatigue, no skin changes, no bleeding or easy bruising, no change in urine/stool. Dyspnea with modest exertion. Normal menses.
Physical Exam

36.8, 118/81, 84, 18
Gen - sitting in chair in NAD
HEENT - anicteric, OP clear without erythema or exudate, pale conjunctivae
Neck - supple without LAD
Lungs - clear to auscultation
Heart - regular, no murmur, no lee
Abd - soft, no splenomegaly
Skin - no petechiae, questionable jaundice of chest
Labs

- Hemoglobin – low
- MCV - low
- Iron - low
- Ferritin - normal
- Transferrin saturation - low
- Reticulocyte count - low
- WBC – low normal
Labs

- Anti-endomysium antibody - negative
- Indirect bilirubin - normal
- Haptoglobin - normal
- LDH – normal
- Peripheral smear - hypochromic, microcytic RBCs
- Endoscopy - negative
Global Prevalence of Anemia

Lancet 2011; 378:2123–2135
Causes of Anemia in Low or Middle Income Countries

Genetic haemoglobin disorders
- Thalassaemias
- Haemoglobin variants
- Glucose-6-phosphate dehydrogenase deficiency
- Ovalocytosis

Infectious disease
- Soil-transmitted helminths
- Malaria
- Schistosomiasis
- Tuberculosis
- AIDS
- Leishmaniasis
- Tropical sprue
- Malabsorption and disorders of the small intestine

Nutrition
- Iron deficiency
- Folic acid deficiency
- Vitamin B12 deficiency
- Vitamin A deficiency
- Protein energy malnutrition

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Iron Homeostasis

- Majority of iron in plasma from breakdown of hemoglobin in senescent RBC
- + 1-2 mg/day by duodenal enterocytes → plasma or stored as ferritin
- - 1-2 mg/day sloughed enterocytes
- Recycled iron by macrophages loaded onto serum transferrin → marrow

Iron Homeostasis

• Prevent excessive iron absorption in the proximal small intestine
  – Excessive tissue iron $\rightarrow$ organ damage
• Regulate the rate of iron release from macrophages
  – Rapid release $\rightarrow$ create localized tissue injury via generation of reactive free radicals
• Infection (and inflammatory diseases) induce iron sequestration in macrophages and decrease iron absorption in the small intestine
  – Increase in iron intake may decrease host resistance
Iron Homeostasis

Iron supplements can favor pathogens

Optimum nutrient balance for host

Deficit → Impairs host immunity

Excess → Impairs host immunity

Iron availability and pathogen mechanisms for iron acquisition influence niche selection

Host genome (resistance) and pathogen genome (virulence) factors determine optimal nutritional balance

Iron concentration →

Risk of infection

Science 2012; 338: 768.
Hepcidin

- Identified via studies of antimicrobial properties of body fluids
- Isolated in urine
- Site of synthesis (liver) + microbicidal
- Mediator of innate immunity

*Blood 2003; 102: 783-788*
Iron Metabolism
Iron Metabolism

Son of Mothers against Decapentaplegic (SMAD)
Hepcidin
Hepcidin: Mechanism of Action

Haematologica 2006; 91: 727-732
Hepcidin decreases serum iron and dietary iron absorption

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Iron concentration →
TMPRSS6 mutants
“Mask” mouse

- Anemia, microcytosis, iron deficiency, and elevated hepcidin mRNA transcripts
- High doses of iron → hair growth
- Poor absorption of iron from gut
- Mutation on chromosome 15 (transmembrane serine protease – TMPRSS6)
- TMPRSS6 gene suppressed hepatic hepcidin expression

“Mask” mouse

“Mask” mutation

TMPRSS6 (aka matriptase)
Iron Metabolism
Hereditary microcytic iron-deficient anemia

• 1981: Three siblings had iron deficiency anemia
  – No evidence of reduced iron intake or gastrointestinal blood loss
  – Failed to respond to oral iron therapy
  – Partial hematologic response to intramuscular iron dextran

J Pediatrics 1981; 98:723-8
Iron refractory iron deficiency anemia (IRIDA)

- Due to a mutation in the TMPRSS6 gene
- Hypochromic, microcytic anemia
- Low serum iron
- Low transferrin saturation
- Elevated hepcidin levels
Diagnosis

- Sequencing of exons and exon-intron boundaries of TMPRSS6 gene
- SNaPshot assay – screening of several iron-related gene mutations
- Combined PCR and high resolution melting (HRM) assay
- Next-generation sequencing
TMPRSS6 mutation heterogeneity

• At least 40 different mutations reported
  – Missense
  – Nonsense
  – Frameshift
  – In-frame deletion
Treatment

- Parenteral iron
Future Therapies?

- Anti-hepcidin antibodies
- Genetically modified lipocalins
- PEGylated anti-hepcidin L-RNA oligonucleotide


THANKS!