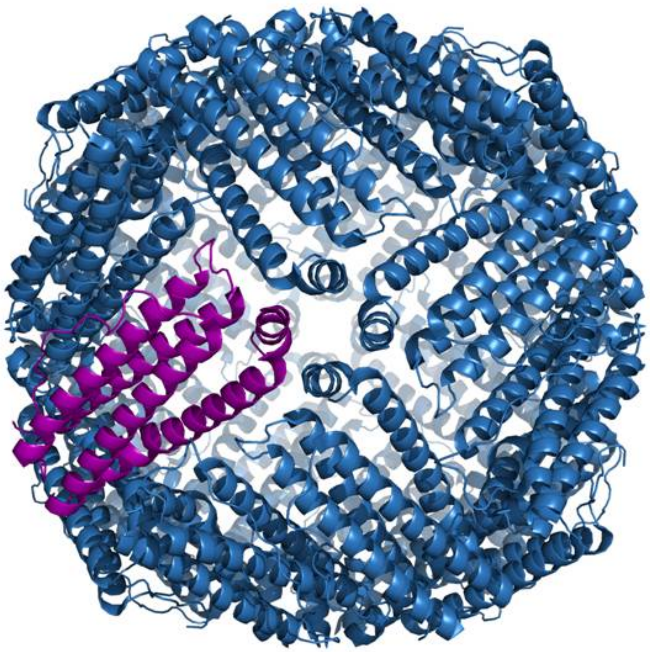
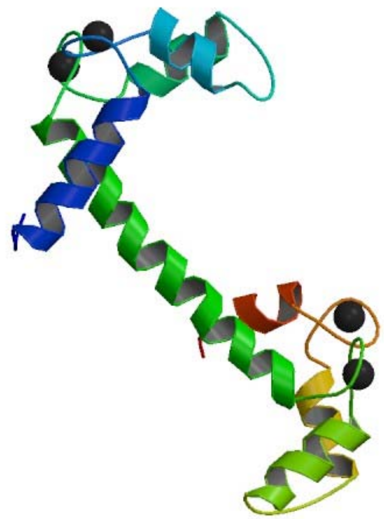
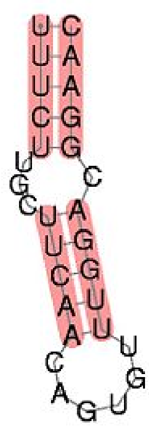
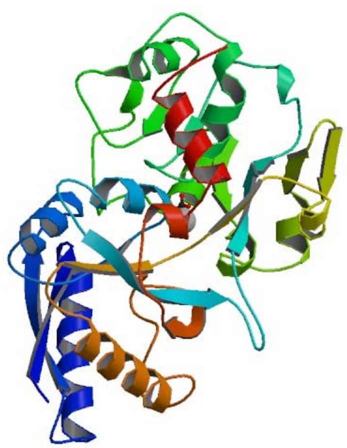
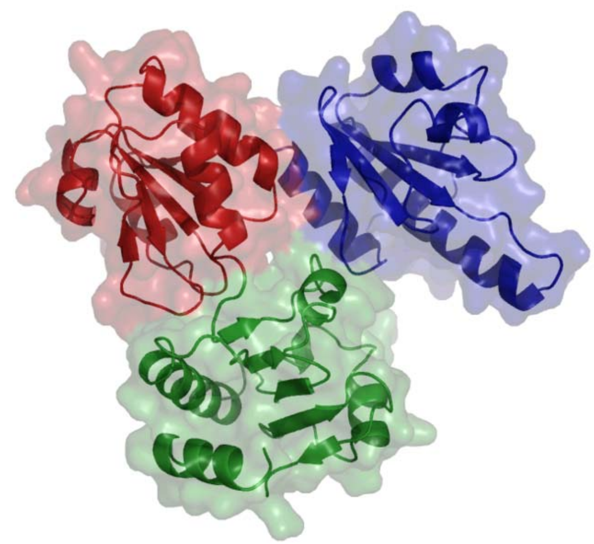
Iron and Calcium Metabolism





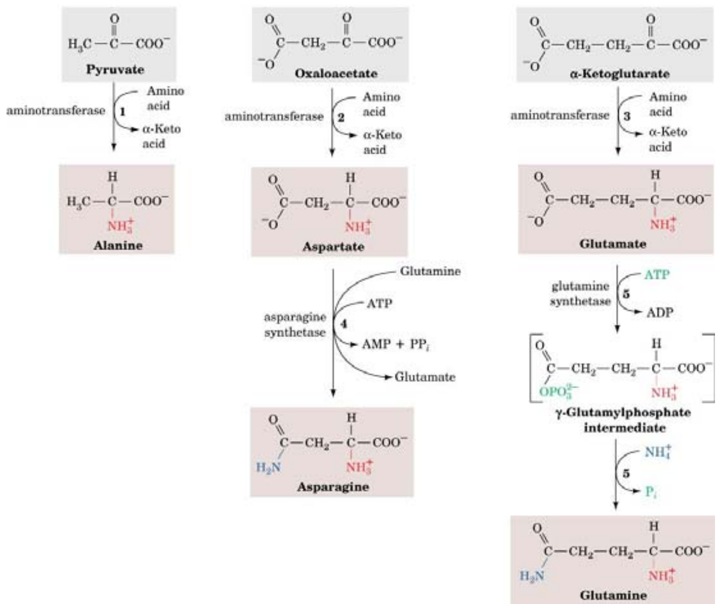




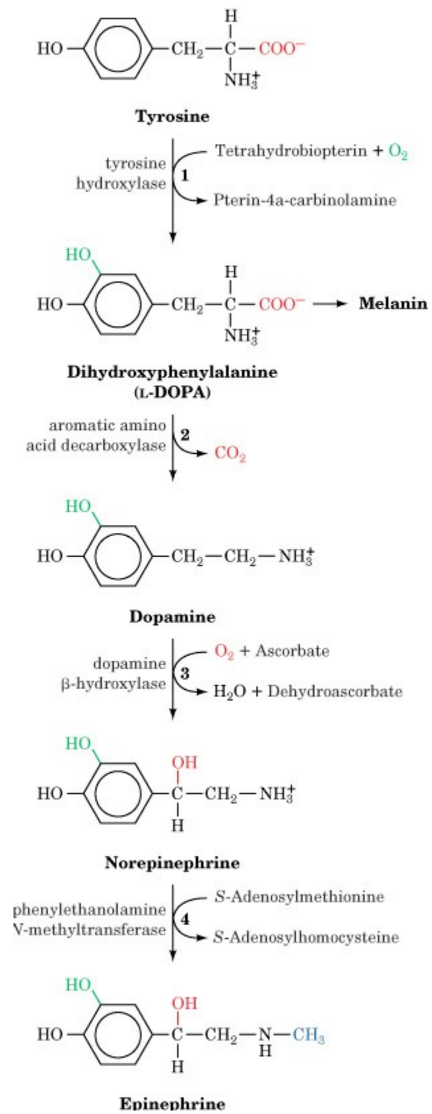


Last Week: Amino Acid Metabolism

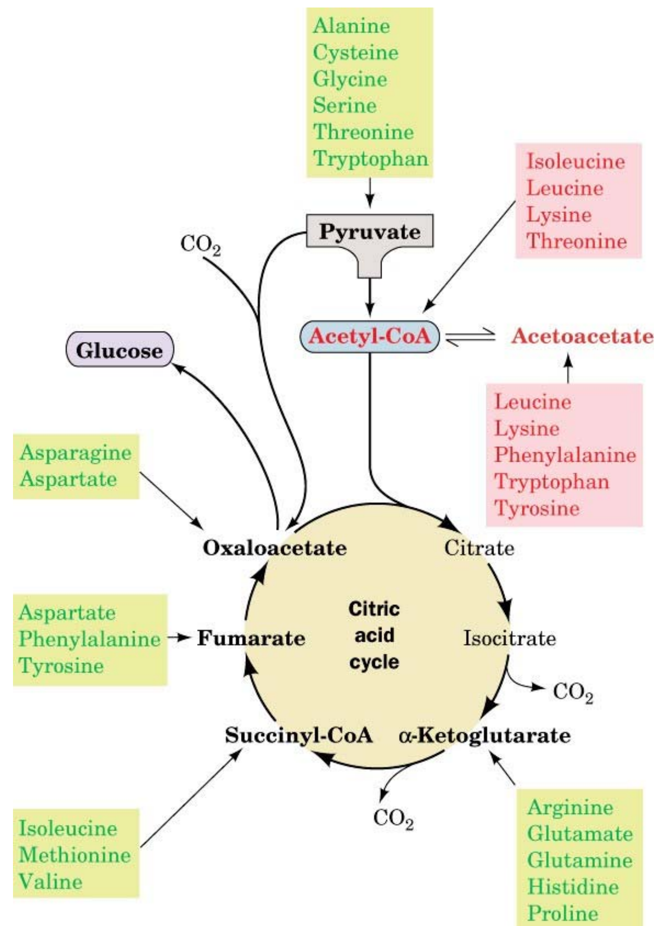
Build 'em up



Use 'em

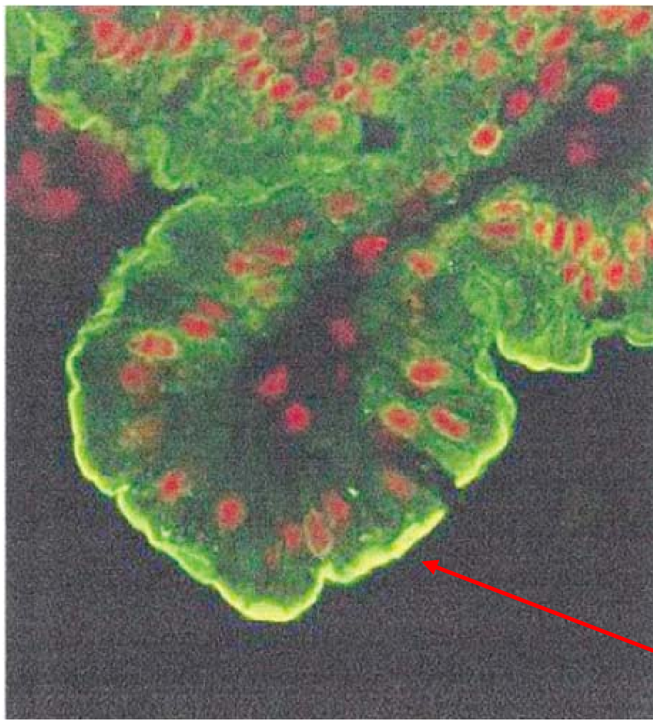


Break 'em Down



Iron Metabolism Step 1: Getting it in!

- Most dietary Iron is in the Fe^{3+} (oxidized) state. But the transporter used to get iron across the cell membrane, Divalent Metal Transporter 1, can only trasnport Fe^{2+} through the intestinal mucosa.



Blood Cells, Molecules, and Diseases Volume 29, Issue 3, (2002) Pages 356-360

- Reduction is accomplished via a ferric reductase enzyme that hangs around the brush border membrane of enterocytes (in your gut).

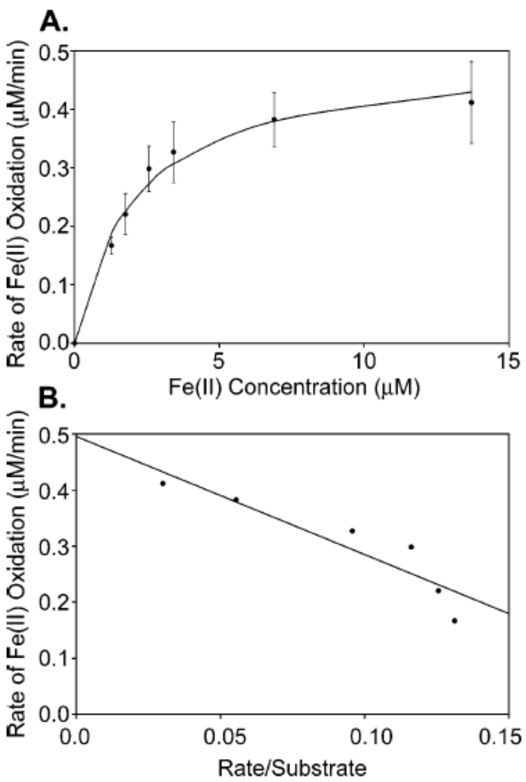
- The critical ferric reductase is controversial but it may be duodenal cytochrome B

Seems to be located in about the right place! (bright green)

The Other Side of the Enterocyte

- On the other side of the Enterocyte is an Iron specific transporter Ferroportin, but it only takes Fe^{3+}!

- To re-oxidize we use the oxidoreductase Hephaestin, which is multi-copper enzyme



A nice Michaelis-Menten plot!

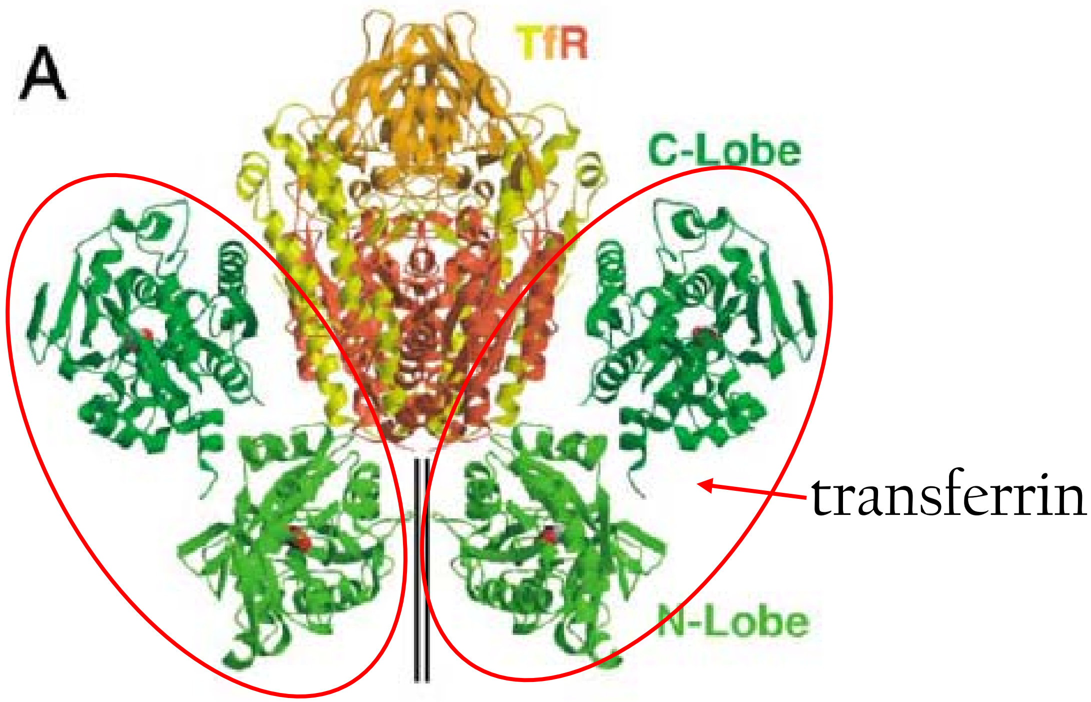
- The newly oxidized and transported Fe^{3+} is picked up (directly from the transporter) by Transferrin.

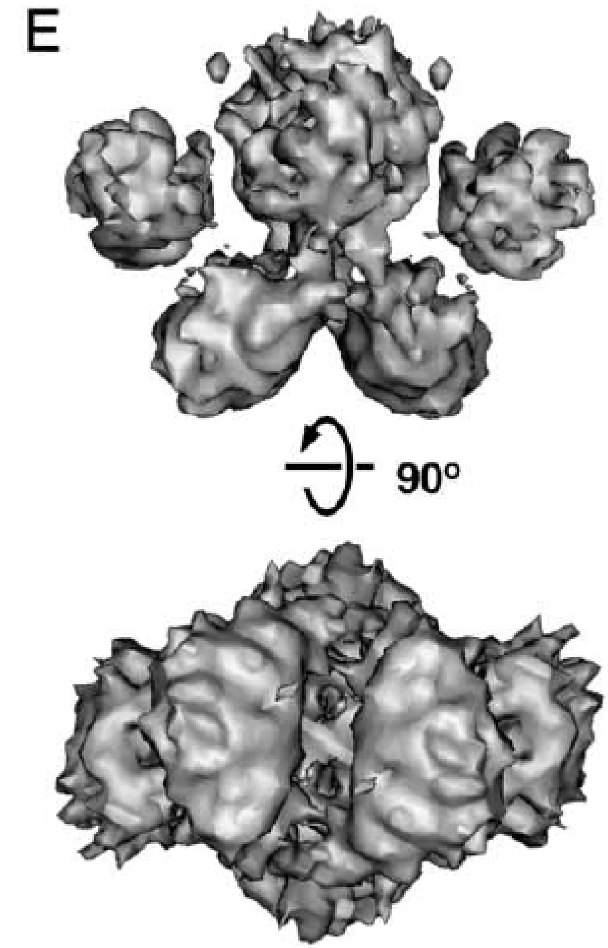
Biochemistry **2005,** *44,* 14725-14731

Transferrin

- Transferrin is responsible for circulating insoluble Fe^{3+} in the plasma

- Cells pick up circulating transferrin using transferrin receptor (TfR)

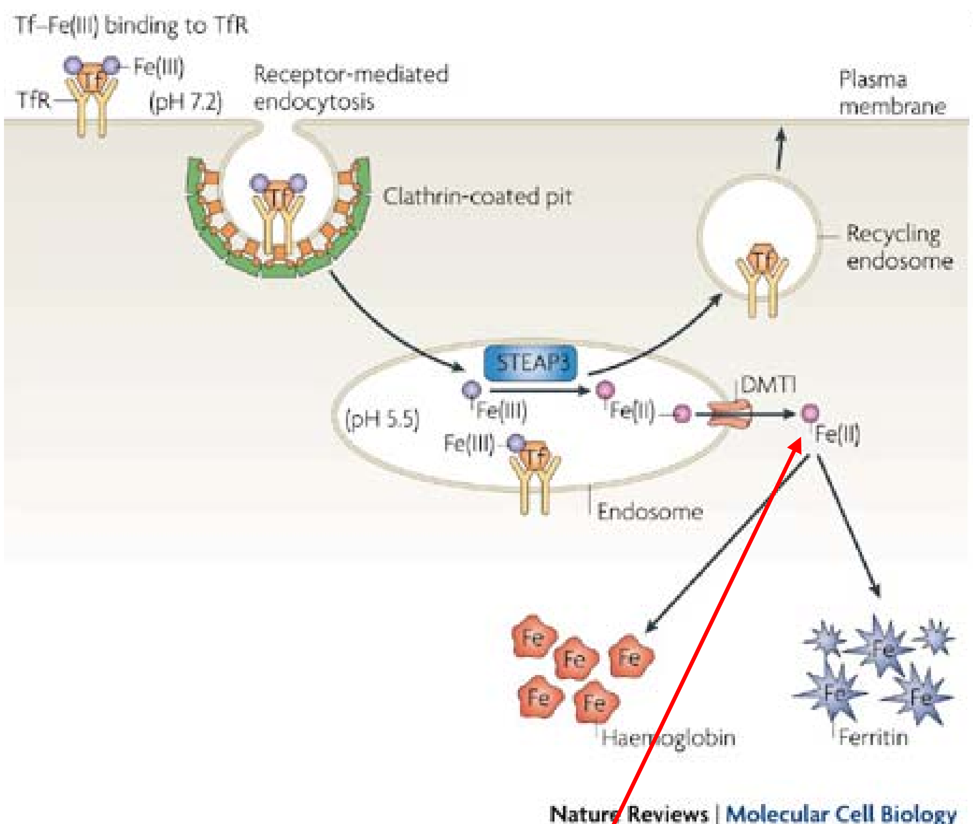




Cell, Vol. 116, 565–576, 2004

Getting Iron Into the Cytoplasm

- When bound to Transferrin, TfR promotes receptor mediated endocytosis, forming an Endosome



ROS-maker!! Turns H_2O_2 into OH•

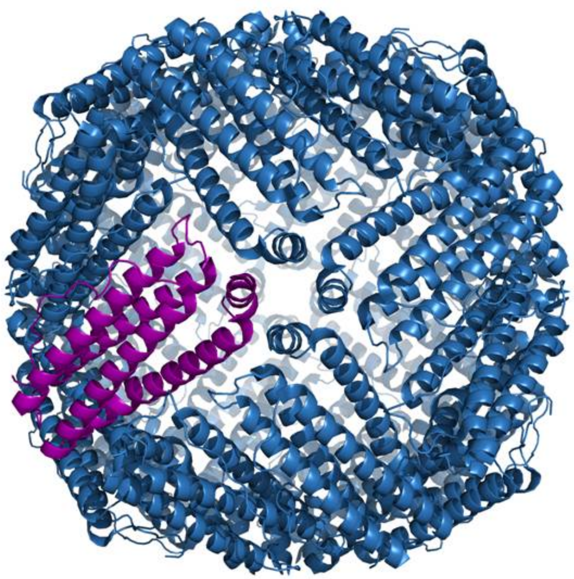
- In the endosome, Fe^{3+} is reduced to Fe^{2+} so that it will not precipitate in the cytoplasm

- Removed from endosome via Divalent Metal Transporter (DMT) 1.

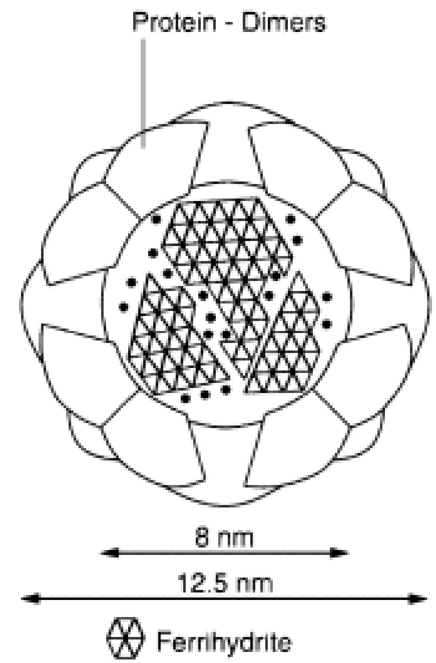
- From there the iron can be directly incorporated into Hemoglobin, or go into storage in Ferritin

Ferritin

- Ferritin is the body's massive (480 kDa) iron storage protein



- Inside the Ferritin sphere, iron is made to crystalize with OH and some phosphate in a manner similar to the mineral ferrihydrite: $Fe_5HO_8 \bullet 4H_2O$



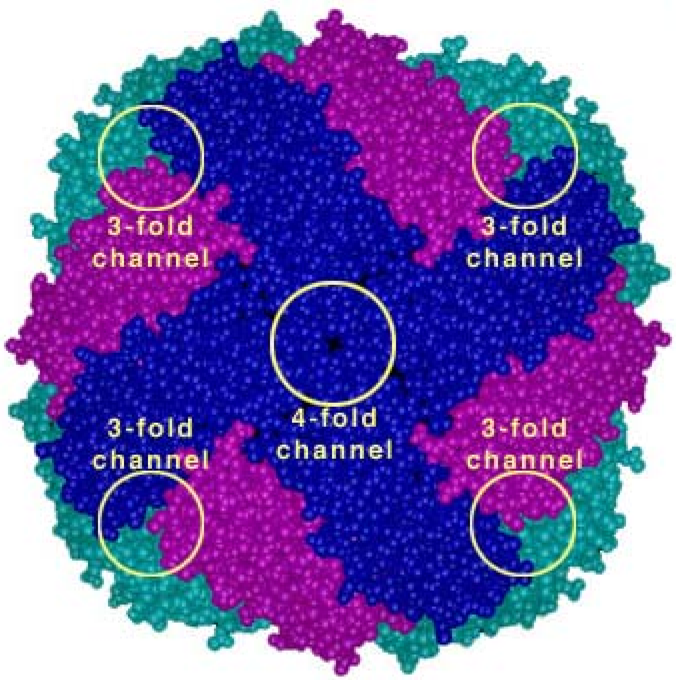
- Iron is stored as Fe^{3+}

- Each Ferritin can hold about 4500 iron atoms

- Serum levels of Ferritin are roughly proportional to the amount of iron available, and are therefore diagnostic of anemia.

Release of Iron from Ferritin

- OK, so we've got our iron in storage. How do we get it out?



- We can release Fe^{3+} from the ferrihydrite crystal by reduction to Fe^{2+}

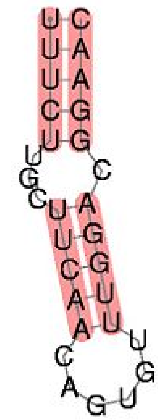
- Reduction occurs somehow, probably via an electron transfer through the 4-fold channel

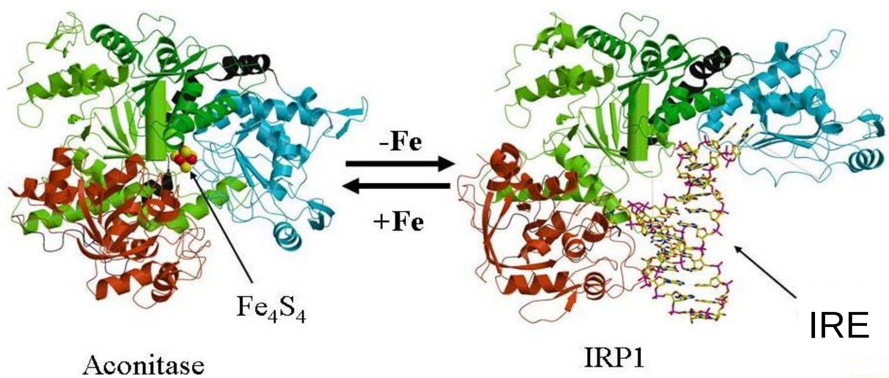
- After reduction, Fe^{2+} leaves via the 3-fold channels, which contain solvating charged amino acids.

http://www.chemistry.wustl.edu/~edudev/LabTutorials/Ferritin/Ferritin.html

Regulating Iron Levels in the Cell: IREs

- Iron Responsive Elements (IREs) are RNA stemloops that are present in the untranslated regions of the mRNAs of iron metabolism associated proteins

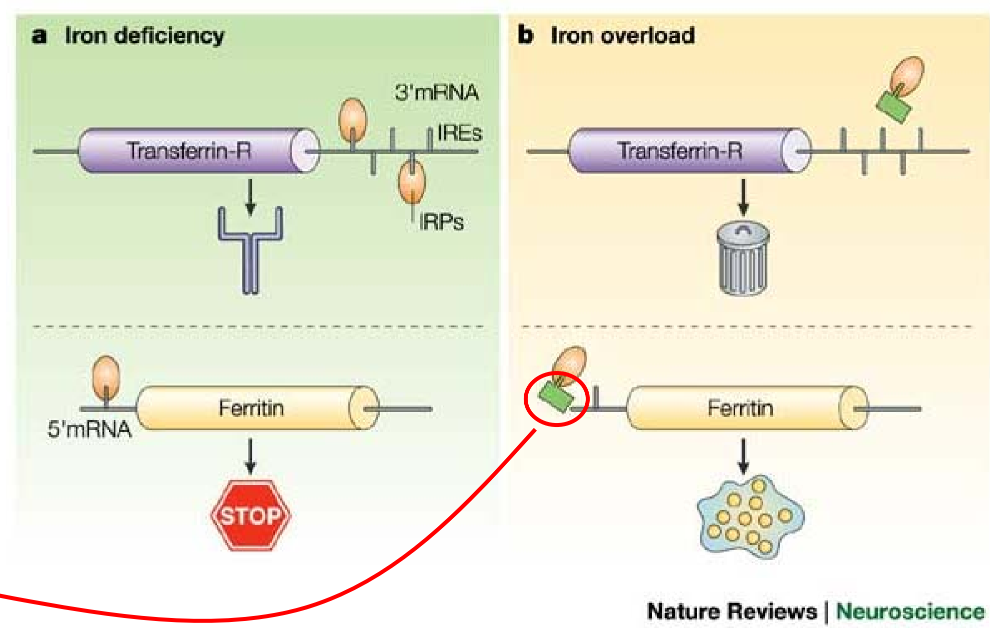




- IREs are stabilized by Iron Responsive Proteins (IRPs) which have FeS clusters.

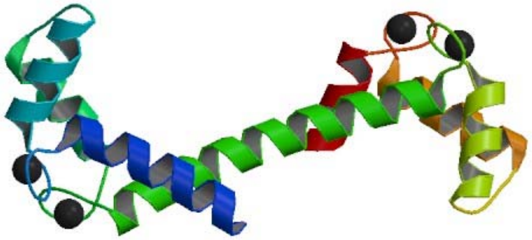
- IREs protect the TfR mRNA from degradation! Fe↓, TfR↑

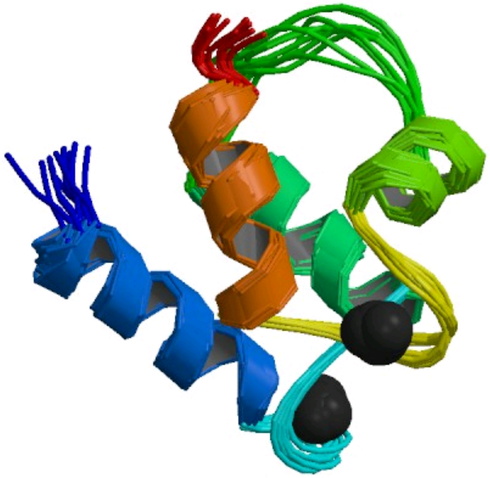
- IREs prevent translation of ferritin mRNAs! Fe↓, Ferritin↓

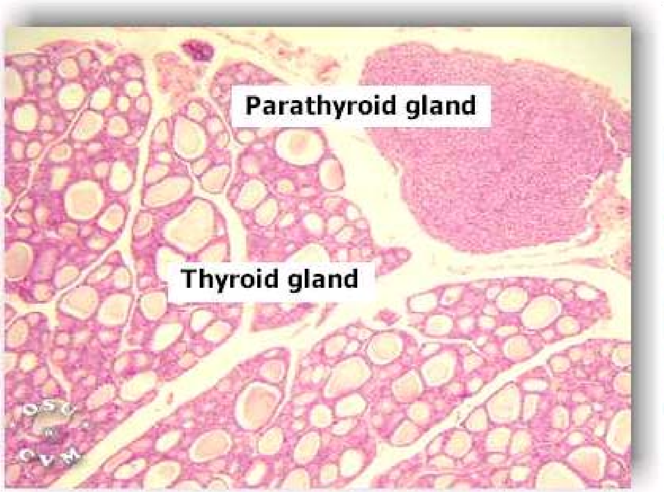


FeS cluster prevents binding/stabilization!

Calcium Metabolism







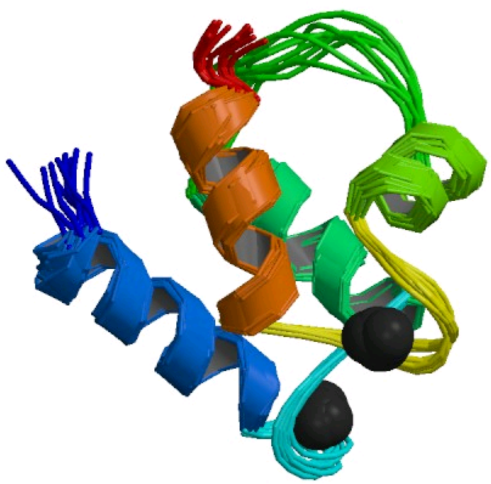
Uses of Calcium

- Uses of calcium include:
  - Bone
  - Neutrotransmission to Muscle Contraction: Voltage gated Ca^{2+} transporters cause Ca^{2+} to be rapidly taken up by neurons, causing the release of acetylcholine into the synaptic cleft
  - Cell cycle: Calcium affects the activity of – Mitosis promoting factor, CaM Kinases and inositol triphosphate

Calcium Metabolism Step 1: Getting it in there!

- Dietary sources of calcium:
  - Milk
  - Cheese
  - Sardines
  - Fortified orange juice
  - Fortified cereal
  - Fortified soy

- Calcium is absorbed through enterocytes in the small intestine



Calbindin: Binds Ca^{2+} in gut

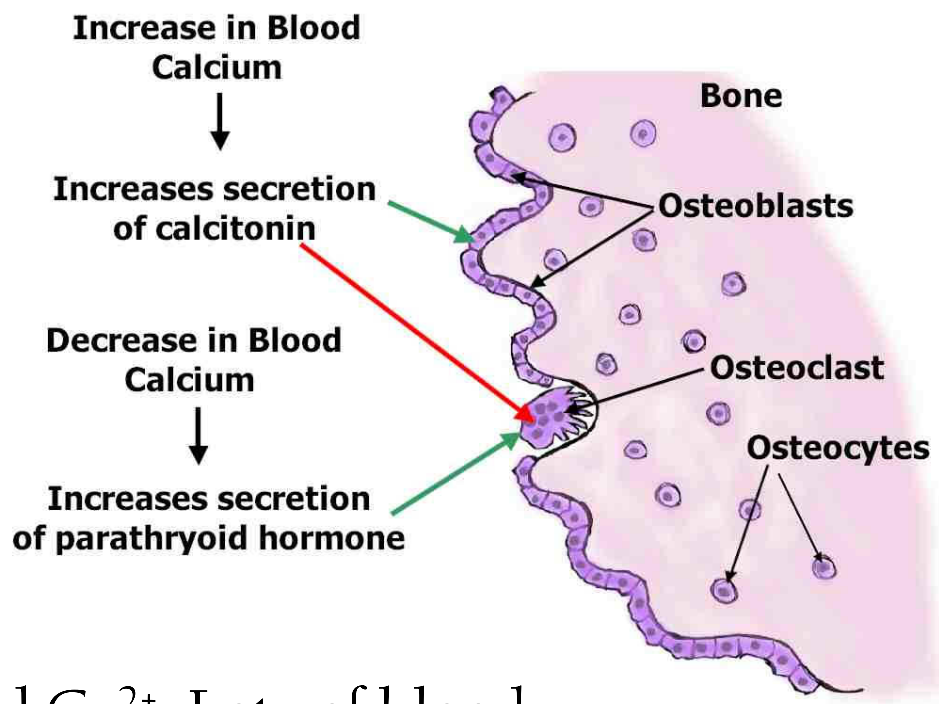
Transient Receptor Potential Vanilloid 6: Binds Ca^{2+} in gut (soluble domain above)

Calcium in the Blood

- Unlike iron, Ca strongly prefers the 2+ oxidation state, which is soluble.

- So, unlike for iron, we don't have to worry about going back and forth between soluble and insoluble oxidation states

- This means we can keep lots of free Ca^{2+} in the blood (1 mM), although roughly half of extracellular Ca^{2+} is protein-bound

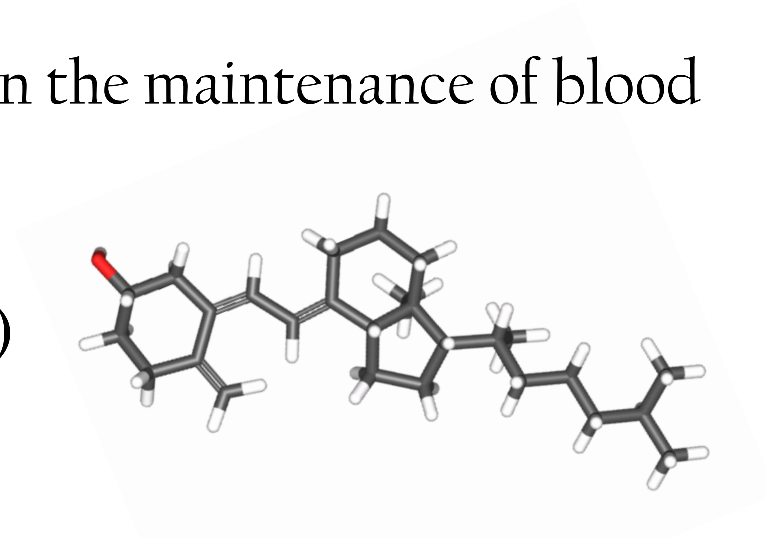


- The counterion of Ca^{2+} in the blood is phosphorous

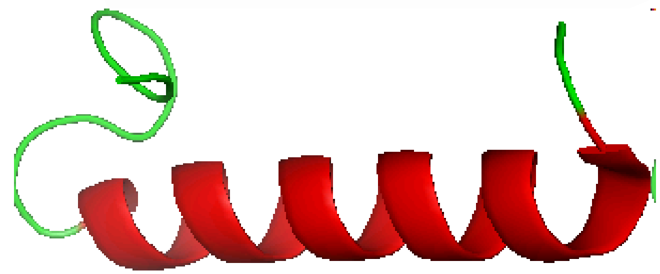
- Bone acts as a resevoir of blood Ca^{2+}. Lots of blood calcium increases uptake of Ca^{2+} by osteoblasts

Control of Blood Calcium

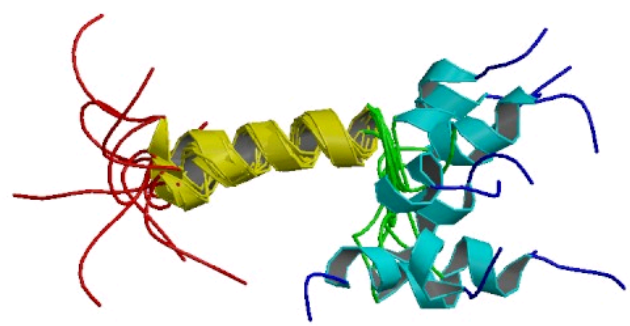
- There are three main players in the maintenance of blood calcium levels:



- Vitamin D (calcitriol)



- Calcitonin
  (Blood Ca^{2+} ↓)

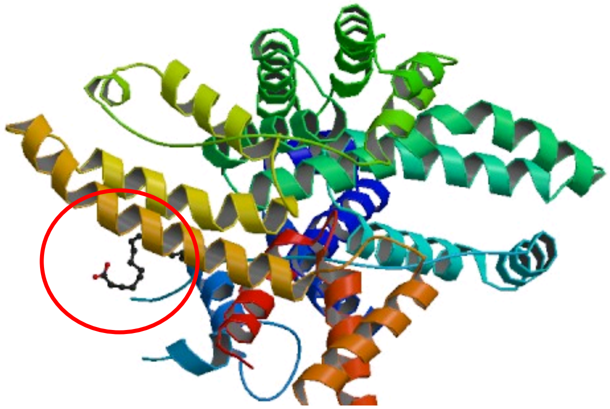


- Parathyroid Hormone
  (Blood Ca^{2+} ↑)

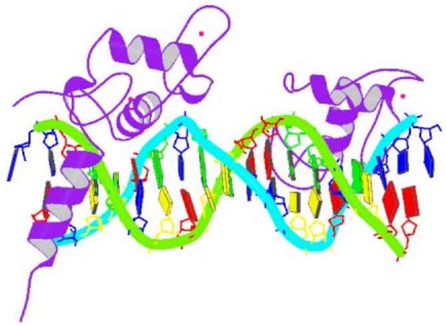
The Role of Vitamin D

- A vitamin D precursor is synthesized from cholesterol which is converted to previtamin D_3 by UV light in the skin. After an isomerisation, vitamin D_3 is sent to the liver and the kidneys where it is hydroxylated to Calcitriol, the bioactive molecule.

- Calcitriol is transported around in the plasma by an albumin protein – Vitamin D binding protein



- Uppon binding vitamin D, Vitamin D receptor acts as a promoter for calbindin and TRPV6 (see three slides up) among other calcium related genes



The role of Vitamin D part II

- So vitamin D upregulates uptake of calcium in the gut by upregulating calbindin and TRPV6

- Also inhibits parathyroid hormone release from the parathyroid gland resulting in a higher level of uptake of Ca^{2+} in osteoblasts

This promotes bone mineralization (maintenance) and regrowth

- Vitamin D deficiency causes:
  - Rickets
  - Osteomalacia
  - Osteoperosis

Bone =:

Hydroxyapatite, calcium carbonate and calcium phosphate

The Parathyroid

Doctor, doctor in your green coat
Doctor, doctor cut my throat
And when you've cut it, doctor then
Won't you sew it up again

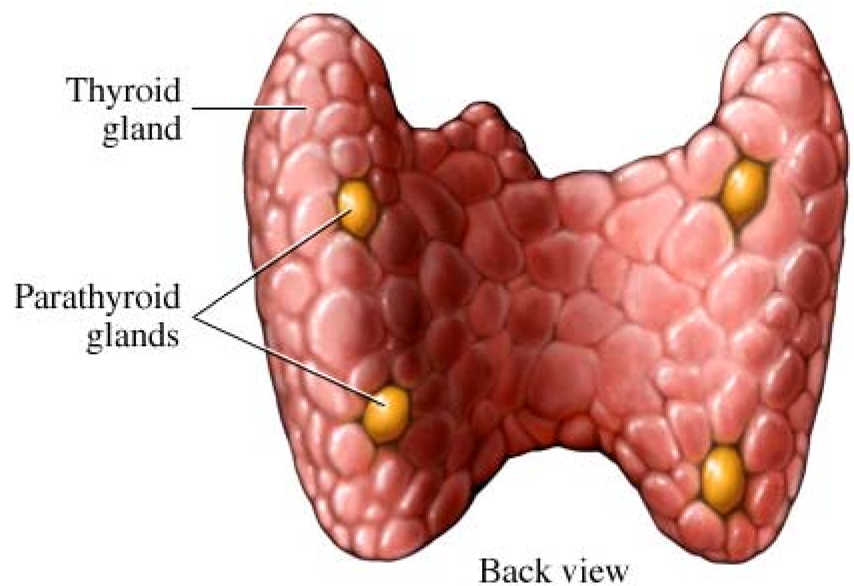
- **Isaac Asimov** (about to get a thyroidectamy)

- The parathyroid is a set of small nodules on the thyroid gland

- Parathyroid hormone stimulates production of Vitamin D

- Reduces excretion of calcium in urine

- Stimulates osteoclasts to release Ca^{2+} from bone.



Calcitonin

- Calcitonin is produced in a variety of tissues, but mainly in the thyroid

- Supresses digestion of mineralized calcium in bone by osteoclasts, reducing Ca^{2+} in blood

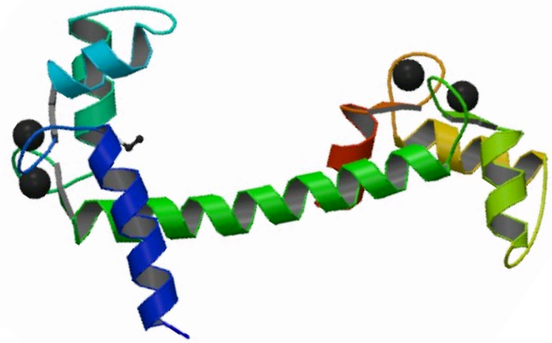
- Promotes loss of Ca^{2+} via the urine by preventing reuptake of Ca^{2+} in tubules in the kidneys

- The role of calcitonin is still a little unclear – some evidence shows that large does of calcitonin have little effect on blood calcium in humans

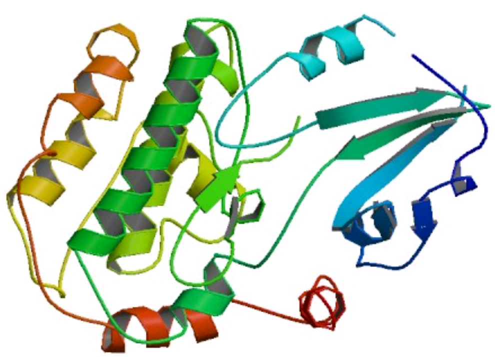
Intracellular Calcium Metabolism

- In cells, calcium levels are an important metabolic determinant

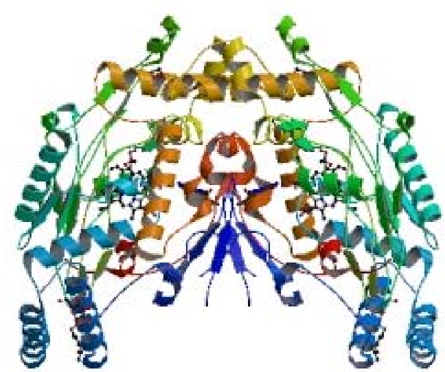
- The predominant 'calcium sensor' protein in mammals is calmodulin (CaM)



- Examples of target proteins



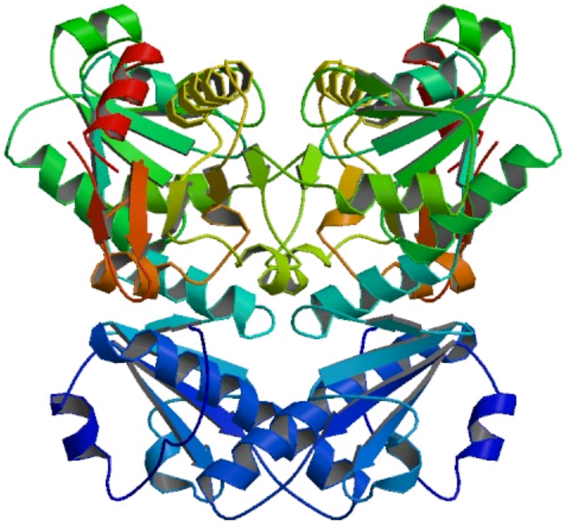
CaM dependent protein kinase



Nitric Oxide Synthase

Calcium Storage and Transport

- Calcium can be kept freely in the cytoplasm, but it must be balanced by a counterion… to keep an excess of Ca^{2+} around, for when it is needed calcium is stored bound to Calsequestrin



- Calcium can be transported directly into cells from the blood. There are a number of calcium transporters including a Ca^{2+} channel, a Ca^{2+}/Na^{+} exchanger and an active ATPase Ca^{2+} transporter.

- Calcium is actively transported into mitochondria mostly through a sodium gradient (i.e. a Ca^{2+}/Na^{+} transporter).