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Abstract:
The biology of iron transport is dictated by the chemistry of iron. Free iron is present around 10^{-10}M in water at neutral pH (in an oxygenated solution) and around 10^{-19}M in the presence of phosphate buffers, concentrations too low to support cellular viability. Consequently, from the moment iron is liberated from food sources, to its final distribution in the cell, iron must be "handed-off" from one chelator to another chelator. Failure of chelation, which is tantamount to the presentation of iron to reducing or oxidizing agents, results in reactive chemistry, while appropriate chelation solubilizes and protects iron from changes in oxidation state. In the past decade, a series of iron chelators, carriers and transporters (both proteins and organic molecules) have been identified which affect the exchange of iron from the gut lumen to nearly every cell of the body, even at neutral pH, in the presence of oxygen. These proteins and organic molecules provide both short range transport (across cell membranes) and long range transport (through the circulation) to deliver adequate amounts of iron to target cells and recycle iron from damaged cells. Almost no iron is lost to the environment meaning that the steady state can be maintained with limited replacement (approximately 1mg per day in humans). This means the capture and trafficking pathways are efficient and export of iron to the environment is contained. Mechanisms that capture and recycle iron have been described and have been most importantly studied in duodenal enterocytes or macrophages. Yet, a number of proteins which carry iron are filtered into the nephron, and acute and chronic kidney injury is well known to result in the appearance of iron in the urine, resulting in catalytic iron mediated damage. To understand iron trafficking in the kidney requires an analysis of iron trafficking proteins in many cell types along the course of the nephron. I have identified both canonical and non-cannonical localizations of these proteins in the nephron and I propose to understand how they remove iron from the urinary space and transport it safely to the blood. My lab has the expertise and all of the standard tools required for these studies, such as a series of floxed-iron transporter genes, novel Cre Drivers, and tracers loaded with iron, to detect the location of cellular and urinary iron when different transporters are deleted. Our preliminary results suggest that both proximal and distal nephron mechanisms are at play to capture iron including entirely unexpected mechanisms of luminal iron traffic. The preliminary results also suggest that renal iron traffic may be under control of hepcidin, meaning that like the liver, duodenum, and macrophage, the kidney is engaged not only in local iron trafficking but is likely to be a contributor to systemic iron balance. Results from the proposed study will provide molecular implications for iron-mediated damage in acute kidney injury.