Hey, you out there,
raise your hand if you've heard of soluble transferrin receptors.

OK, OK, hematologists lower your hand. Yes, you've probably ordered soluble transferrin measurements at some point in your life to distinguish between iron deficiency anemia and anemia of chronic disease. You guys (or y'all as we say here in the South-ish) can sit this one out for a bit while the rest of us come up to speed on the subject.

Receptors are proteins that are typically found embedded in the surface of cells and their role is to recognize and bind things. Once bound to these things, the receptor may transmit signals to the inside of the cell causing some type of cellular transformation, as in a hormone receptor. Alternatively, once the receptor binds to its thing, both the thing and the receptor can be brought into the cell and in this way receptors are used as a means of delivering certain cargos to cells; as is true for transferrin receptors.

As their name implies transferrin receptors recognize and bind transferrin. But it is not transferrin *per se* that cells covet, but the iron bound to the transferrin. Transferrin, as the name "trans-ferrin" implies, plays an important role in transporting iron within the blood. Under normal circumstances this could be dietary iron taken up from the gut, which is transferred by transferrin to erythroid progenitor cells where it would be used for the synthesis of hemoglobin. For these precursors to take up iron/transferrin complexes, the progenitors must have transferrin receptors on their surface. Once internalized, the iron is released from transferrin and used for hemoglobin synthesis. Iron taken into cells that is not used for specific purposes like hemoglobin production can be stored bound to the protein ferritin.

As important as transferrin receptors may be on the cell surface, our interest here is on soluble transferrin receptors (because they are easier to measure). Soluble transferrin receptors are derived from receptors on the cell surface by having the bonds that anchored them to the cell surface cleaved by some unknown assailant. These soluble transferrin receptors, as far as I know, have no known biological function in the circulation. Nevertheless, their measurement is used clinically as a substitute for ferritin measurements to monitor iron levels in individuals with chronic inflammation where ferritin measurements are of little value (ferritin measurements of dubious value in monitoring iron levels, sound familiar???).

Our focus on soluble transferrin receptors arises from a recent publication in the *British Journal of Hematology* [1]. This manuscript addresses a topic of immense importance to transfusion-dependent DBA patients and their families: iron overload and its complications.

I have discussed the problem of iron overload in transfusion-dependent DBA patients many times in this forum. We have discussed:

- that iron overload and its complications are a significant cause of morbidity and mortality in DBA patients (April, 2012).
- the basic science underlying iron uptake and disposition in the human body (August, 2013).
- that there appears to be something different about the way DBA patients load and store iron relative to other patients receiving a similar number of transfusions (April, 2014).
- and the need for further understanding of iron loading in DBA patients and whether strategies can be developed to reduce the risks and improve outcomes for transfusion-dependent DBA patients (all of the above).

The encouraging news on these fronts is that there have been several papers published the last year or two that have begun to take a serious look at iron loading in DBA patients, with more recent publications focusing on the mechanisms underlying iron handling and disposition [1-3]. One of these manuscripts is the paper in *BJH* that is focus of this newsletter article.

As I've mentioned numerous occasions, although essential for life iron can also be toxic. Fortunately, most of the iron in the human body is found in a protected state bound to various proteins like hemoglobin, transferrin, and ferritin. Iron that is not found in these protected states can undergo a process called the Fenton reaction and produce highly toxic reactive oxygen species that can cause the organ damage.

A generic term for circulating iron found in this non-protected state is non-transferrin bound iron (NTBI). In their study published in the *BJH*, Porter *et al* investigated the generation of NTBI in three groups of patients with transfusion-dependent anemia. These patients had β-thalassemia major, sickle cell disease, or Diamond Blackfan anemia. All had similar transfusion burdens.

As you know from K-12 science projects, scientific inquiry typically begins with a hypothesis. The *BJH* article differs in this respect in that we know so little about the differences in the way iron is handled in DBA patients relative to patients with other transfusion-dependent anemias that it is difficult to come up with a sound hypothesis to test. Instead the *BJH* article takes a different approach. The author's measured a number of different factors involved in iron transport, utilization, and disposition in the three patients groups to determine what, if anything, differentiated one group from another. The idea was that any differences found between these patients groups could then be used to create testable hypothesis. Thus, this manuscript could be classified as hypothesis generating.

While all patients in the transfused cohorts have increased levels of NTBI caused by the excess iron they are receiving as a consequence of their transfusions, what makes DBA patients stand out from the other patients studied is their extremely low levels of soluble transferrin receptor. In fact, three of five DBA patients had no detectable soluble transferrin receptor. At the present time, the authors are only willing to state that the low levels of soluble transferrin receptor are a reflection of the dearth of erythroid progenitors in DBA patients. The basis for this statement is that since erythroid progenitors have abundant membrane-bound transferrin receptors that are the source of soluble transferrin receptors, a reduction in erythroid progenitors leads to a reduction in soluble transferrin receptors.

One could argue that the finding of low levels of soluble transferrin receptors is somewhat of a tautology for DBA, as we have known for quite some time that DBA patients have few erythroid progenitors. But the authors hint that there may be more to this observation than perhaps simply restating the obvious. They suggest that the low utilization of transferrin iron that occurs in DBA patients because of their low levels of transferrin receptors creates a pathway for excess iron to enter the NTBI pool distinct from other transfusion-dependent patients. This difference may ultimately influence how quickly and where iron is diverted into tissues and so, have a bearing on the differences in iron disposition observed between these patient groups.

This study doesn't really answer any questions about iron overload it DBA patients. But the needle is moving. Investigators are beginning to gather data that are setting the stage for more directed hypotheses on the unique features of iron disposition in DBA patients. Subsequent tests of these hypotheses will shed light into this little understood but terribly important topic in DBA pathophysiology and hopefully lead to improved outcomes for transfusion-dependent patients.

1. Porter, J.B., Walter, P.B., Neumayr, L.D., Evans, P., Bansal, S., Garbowski, M., Weyhmiller, M.G., Harmatz, P.R., Wood, J.C., Miller, J.L., et al. (2014). Mechanisms of plasma non-transferrin bound iron generation: insights from comparing transfused diamond blackfan anaemia with sickle cell and thalassaemia patients. British journal of haematology.
2. Berdoukas, V., Nord, A., Carson, S., Puliyel, M., Hofstra, T., Wood, J., and Coates, T.D. (2013). Tissue iron evaluation in chronically transfused children shows significant levels of iron loading at a very young age. American journal of hematology 88, E283-285.
3. Pospisilova, D., Holub, D., Zidova, Z., Sulovska, L., Houda, J., Mihal, V., Hadacova, I., Radova, L., Dzubak, P., Hajduch, M., et al. (2014). Hepcidin levels in Diamond-Blackfan anemia reflect erythropoietic activity and transfusion dependency. Haematologica 99, e118-121.