Dateline: August 21st 2015, Brussels Belgium

Ding…….that's odd, it is 3:00AM back in the US: who would be e-mailing me now? Ah, it's Jeff Lipton; who happens to be sitting immediately in front of me listening to a talk at the 10th triennial Conference on Ribosome Synthesis. The e-mail is sent to all members of our extended research group, including Adrianna Vlachos, who is also attending the conference sitting along side of Dr. Lipton. The e-mail is short and to the point, we need to check the 5 genes the speaker is talking about for pathogenic mutations in DBA patients whose genes remain to be identified.

As readers of this newsletter are aware, newly diagnosed DBA patients are initially analyzed for potentially pathogenic mutations in known DBA genes and if such mutations fail to be identified, they can enter a research-study using various genome-wide analyses to potentially identify the disease-causative gene in the sea of genetic information that goes into making a human being who and what we are (poetic license used in ignoring the broader contributions of nurture to human development). But for those of us sifting through the reams of G's, A's, T's and C's that constitute genetic data, having good candidate genes for mutations that may give rise to defects in ribosome synthesis similar to known ribosomal proteins affected in DBA is a potential Godsend.

Insights such as these are one of the many reasons why the three of us are attending this meeting and why the Diamond Blackfan Anemia Foundation sees fit to provide financial support for this and other meetings relevant to the health and well being of DBA patients. The talk highlighted by Dr. Lipton was by Dieter Kressler, an investigator at the University of Fribourg in Switzerland. Although he was working in Baker's yeast, what Dr. Kessler was presenting clearly seemed relevant for DBA patients whose genes remain to be identified. His work revealed that many ribosomal proteins must be escorted from their site of synthesis in the cytoplasm to the nucleolus, a sub-compartment of the nucleus, where ribosomal proteins assemble with ribosomal RNAs and other ribosomal proteins to make a ribosome. These protein escorts are referred to as chaperones, which like chaperones at a teenage mixer are there to prevent inappropriate interactions between entities that have yet to reach full maturity. Ribosomal proteins, in particular, seem to be prone to getting themselves in trouble biochemically speaking, if left on their own apart from becoming a part of a functional ribosome. One such troublesome outcome is for the ribosomal protein to aggregate and be destroyed before ever reaching the nucleolus, and therefore being unavailable for ribosome synthesis. So the loss of one of these chaperones could very likely result in the net loss of the ribosomal protein it was there to protect. What was noteworthy from the Kressler talk to the DBA community was that some of the chaperones being discussed happened to be chaperones for ribosomal proteins affected in DBA. And so, or voilà as they say in French speaking areas of Belgium, genes encoding these chaperones become candidates for disease-causing mutations in DBA patients, as the net effects of these mutations should be similar to the effects of mutations in the genes encoding the ribosomal protein they chaperone.

Another part of the meeting directly relevant to the DBA community was an entire session devoted to the two DBA proteins, Rpl5 and Rpl11. These proteins form a complex with 5S RNA, which in addition to eventually becoming an integral part of the ribosome also plays an important role in signaling various types of cellular stress to regulators of p53 amount and activity. For years now, this signaling pathway has been proposed to play an integral role in DBA pathophysiology and the detailed structural and functional insights into this complex presented at this meeting hold promise in developing treatments to temper this signaling and in doing so moderate disease symptoms.

Three additional sessions also had ribosomes and disease as a major focus. One of these was entitled "Ribosomopathies" while the other two were less conspicuous in their link to disease with the titles "Cell Proliferation and Development" and "Specialized Ribosomes." Although perhaps less conspicuous in their relationship to disease, DBA is clearly a disease affecting different aspects of human development manifested through the effects of defects in ribosome biogenesis on cell proliferation at different stages of embryogenesis. Moreover, the concept of specialized ribosomes or ribosomes that differ from one another with respect to their complement of ribosomal proteins, which in turn may give different populations of ribosomes distinctive properties, is gaining traction as a mechanism of human disease, particularly with respect to the potential role of specialized ribosomes in carcinogenesis.

While it was clear from this meeting that the wider ribosome community has much to offer to those of us interested in understanding the molecular basis of DBA, it is also clear that this wider group of investigators can also learn from the DBA community. One of the presentations in the session on ribosomopathies was by our own Dr. Adrianna Vlachos, fresh from her tour de force series of presentations at this year's Camp Sunshine. Her summary of patient characteristics derived from the North American DBA Registry could and should play a critical role in formulating and testing hypotheses as they pertain to the role of ribosome synthesis in human disease. Similar to Johnny Cochran's exclamation "if the glove don't fit you must acquit" in the O.J. Simpson murder case, if hypotheses as to the role of the ribosome in human disease don't fit with patient characteristics, you must acquit yourself of these hypotheses in favor of alternatives that better fit the patient profile. Thus, it is vital that basic scientists gain exposure to the clinical aspects of the disease their research impinges upon.

Research on ribosome synthesis and the molecular basis of DBA have both shown remarkable advances in the last 10 years. These advances mesh every three years when investigators throughout the world get together to discuss the synthesis of this remarkable organelle. The insights gained through fundamental studies on ribosome synthesis from bacteria to humans continue to shed light on what goes wrong in patients where the process no longer functions properly. Learning how processes work normally is often the key to learning how to fix them when they go awry.

Understanding how a ribosome is put together with the myriad of factors involved has been a challenging undertaking that has occupied the time and effort of hundreds of dedicated scientists for over 50 years. It is clear from this year's meeting that these efforts are coming to fruition, which is good news for individuals with DBA and other diseases linked to the ribosome and its synthesis.