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Bone Marrow Failure Syndromes: The Ribosomopathies

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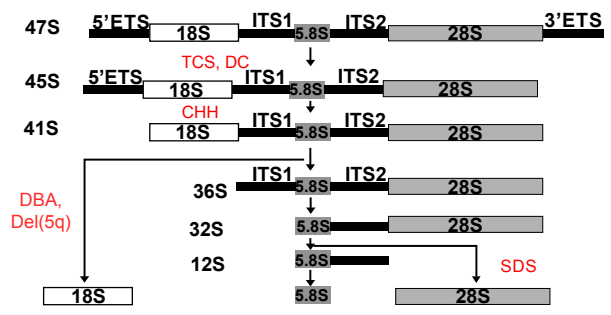
In recent years a number of human diseases associated with dysregulated ribosome biogenesis have been identified and categorized as "ribosomopathies" [1]. Acquired or congenital genetic lesions leading to impaired ribosome biogenesis and function appear to be germane to this class of disorders that include Diamond-Blackfan anemia (DBA), a disorder characterized by pure red cell aplasia, Shwachman-Diamond syndrome (SDS), dyskeratosis congenita (DC), cartilage hair hypoplasia (CHH), Treacher Collins syndrome (TCS), and del (5q), a type of myelodysplastic syndrome (MDS). While each of these disorders is associated with distinct mutations in the ribosome biogenesis pathway (Figure 1), bone marrow failure appears to be a uniformly observed clinical symptom. However, the affected lineages appear to be uniquely syndrome-specific. For example, the erythroid and megakaryocytic lineages are affected in DBA and del (5q) MDS, while neutropenia predominates in SDS. From the first identification of disruption of RPS19 (ribosomal protein small subunit 19) in a DBA patient by Dahl et al. [2], limited advances have been made in our understanding of the molecular underpinnings of bone marrow failure syndromes [3].

Ribosome Biogenesis and Disease

The human ribosome is a complex Ribonucleoprotein (RNP) supermolecule composed of four ribosomal RNAs and 79 different ribosomal proteins that assemble into a cellular platform for protein synthesis. Ribosome biogenesis occurs in the nucleolus, a nuclear substructure that harbors multiple pre-rRNA genes arranged in tandem. The transcription factors SL1, UBF and RNA polymerase 1, as well as a large family of small nucleolar RNAs, participate in a highly coordinated series of events involving specific cleavage of the pre-rRNP particles (Figure 1). This leads to the formation of the 40S or small ribosomal subunit containing 18S rRNA and the 60S or large ribosomal subunit containing the 28S, 5.8S and 5S rRNA species [4]. Following assembly, the large and small ribosomal subunits are exported to the cytoplasm where protein synthesis ensues. The primary function of ribosomes is to direct the translation of mRNAs into protein. Complete loss of expression of genes encoding ribosomal components has never been described in humans, suggesting that these proteins are so vital to normal cellular function that such mutations are embryonic lethal. However, in *Drosophila* and mammals, haploinsufficiency of some ribosomal proteins leads to a ribosome deficit that decreases the cell's translational capacity. In *Drosophila*, the resultant mutants have a growth restricted phenotype, and are referred to as minute [5]. While it had been known that alterations in ribosome function can alter cell homeostasis, it was not till the discovery of RPS19 being the causative agent of DBA that the role of ribosomes in disease came into focus.



In red, diseases associated at the steps indicated

Figure1: Schematic showing ribosomal RNA processing from the 47S pre-rRNA species to the mature 18S. 5.8S and 28S rRNAs.

DBA Shows the Way

Haploinsufficiency of Ribosomal Proteins (RP) has been shown to be the common basis for the anemia observed in both DBA and in del (5q) MDS. DBA is a congenital bone marrow failure syndrome characterized by a profound macrocytic anemia. In addition to bone marrow defects, approximately 30-50% of DBA patients have craniofacial, genitourinary, cardiac and limb abnormalities suggesting that DBA is a disease affecting a broad range of developmental features. In addition, DBA shares many of its clinical symptoms, especially erythroblastopenia, with other syndromes such as Shwachman-Diamond syndrome (SDS), cartilage-hair hypoplasia syndrome and dyskeratosis congenita (DC) and del (5q) MDS. More than half the patients with DBA have been shown to have a heterozygous loss of an RP gene, with RPS19, a component of the 40S ribosomal subunit, being the most frequently mutated. The finding that mutations in a ribosomal protein were the underlying cause of the anemia of DBA, was both unexpected and surprising. It remains unclear why defects in ribosomal proteins (RPs) have such a specific and profound effect on erythroid maturation. A number of hypotheses to explain the link between ribosomal protein haploinsufficiency and defective erythropoiesis have been proposed. The most compelling of these proposes that defects associated with ribosomal RNA processing associated with RP haploinsufficiency results in defective ribosome biogenesis, resulting in reduced mRNA translation. Since RPS19 plays a role in the maturation of the 40S ribosomal subunit, haploinsufficiency of this protein in DBA would be expected to result in reduced ribosome levels in all cells. However, since late stage erythroid cells are thought to undergo rapid cell division coupled to an enormous translational demand for globin synthesis, such a decrease may be more acutely disruptive to the translational machinery in erythroid precursors. This hypothesis has recently been tested in both DBA patients and in animal models of DBA treated with the branched chain essential amino acid L-Leucine. L-Leucine positively regulates signaling through the mammalian target of rapamycin complex 1 (mTORC1) pathway, thereby promoting cap-dependent mRNA translation [6]. The anemia associated with DBA was shown to be partially alleviated in both L-Leucine treated zebrafish and

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in mice rendered deficient for RPS19 [7,8] suggesting that the effects of RP deficiency can be improved, in part, by elevating mRNA translation. L-Leucine has also been shown to improve some of the developmental defects associated with DBA as well as the anemia associated with del (5q) MDS [6,7]. However, whether it can improve the cytopenias associated with other bone marrow failure syndromes remains to be determined.

The first line of therapy for patients with DBA has been treatment with steroids. However, only 80% of patients respond to steroids initially and less than half can be maintained on this therapy for extended periods [8]. Non-responders to steroid therapy undergo regular blood transfusions and require additional iron-chelation therapy to prevent hemochromatosis. The only definitive therapy for DBA patients is allogeneic bone marrow transplantation. However, infections and graft-versus host disease contribute to significant morbidity and mortality following transplantation, thus the need for other novel therapies, including the oral use of L-Leucine, clinical trials for which are ongoing in the Czech Republic and about to commence in the United States.

Do Mutant Ribosomes Promote Malignancy?

The p53 tumor suppressor pathway is known to play a critical role in the pathophysiology of the ribosomopathies. The leading hypothesis is that ribosomal haploinsufficiency leads to disrupted ribosome biogenesis with an accumulation of free ribosomal proteins that bind MDM2. MDM2 is an E3 Ubiquitin ligase that normally binds to and targets p53 for proteosomal degradation. The consequent accumulation of p53 leads to cell cycle arrest and apoptosis, which ultimately results in anemia. Several animal models have shown that the anemia associated with RP haploinsufficiency is almost completely alleviated in a p53 null background. However, therapies designed to modulate levels of p53 in an RP-deficient background must be viewed with caution as reducing p53 levels may itself contribute to malignancy. In this context, our group and others have shown that p53-independent pathway(s) also contribute to the anemia associated with RP haploinsufficiency. This may provide a window of therapeutic opportunity for bone marrow failure syndromes associated with the up regulation of p53. It should be noted that L-Leucine has recently been shown to deliver its therapeutic benefits in a p53-independent manner, as measured in both zebrafish and *in vitro* human cell models of DBA [9].

Increased cancer susceptibility has been observed in all the ribosomopathies described to date [10]. While the upregulation of p53 may explain some of the pathological symptoms associated with RP-hapolinsufficiency in DBA, the molecular underpinnings of cancer susceptibility remain unclear.

Deregulation of the translation machinery leading to perturbation of specific mRNA networks associated with cellular transformation, has been touted as an underlying cause for cancer susceptibility in DBA and other bone marrow failure syndromes [11]. The possibility of RPs exerting extra-ribosomal functions and contributing to mRNA translation has been suggested and may contribute to cancer susceptibility. In this context, a recent study has demonstrated that the ribosomal protein RPL38 regulates the translation of the developmentally vital Hox genes, dysregulation of which can lead to malignant transformation [12]. More recently it has been suggested that while ribosomes are thought to be highly conserved mRNA translation machines present in every cell in the body, cells may in fact make ribosomes that differ in composition under different growth conditions [13]. This likely leads to ribosomes with altered translation capacities resulting in differential translation of distinct subpopulation of mRNAs. It is thus tempting to speculate that individual RPs may play a more important role in the translational control of specific mRNAs than previously thought, and that haploinsufficiency of some RPs may contribute to malignant transformation, as has been observed in zebrafish, where haploinsufficiency of a few, but not all, ribosomal proteins leads to tumorigenesis [14].

Concluding Remarks

A central and fundamental role for defective ribosome biogenesis in human disease has now been established. However, a number of questions remain unanswered. First, how do defects in ribosome biosynthesis lead to the pleiotropic clinical manifestations observed in bone marrow failure syndromes? For example, while bone marrow failure is common to both DBA and SDS, patients with the former have severe defects in erythropoiesis while patients with the latter have neutropenia. Since it has been suggested that all ribosomes are not created equal, it is tempting to speculate that different ribosome populations exist under different physiological conditions and that hapolinsufficiency of RPs result in altered mRNA translation in a tissue specific manner, thereby contributing to the specific pathophysiology observed in different ribosomopathies. Second, why is the erythroid lineage specifically targeted in DBA and in del (5q) MDS, despite the fact that ribosomes are required by all cells? And lastly, what is the mechanism underlying the cancer susceptibility in ribosomopathies? Answers to these compelling questions will lead to a better understanding of the biology of ribosomopathies that will allow for the future design of novel and safe therapeutic strategies for the treatment of bone marrow failure syndromes.

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