

Diamond-Blackfan Anemia: The dark side of ribosome biogenesis

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Diamond-Blackfan Anemia: a disorder of ribosome synthesis

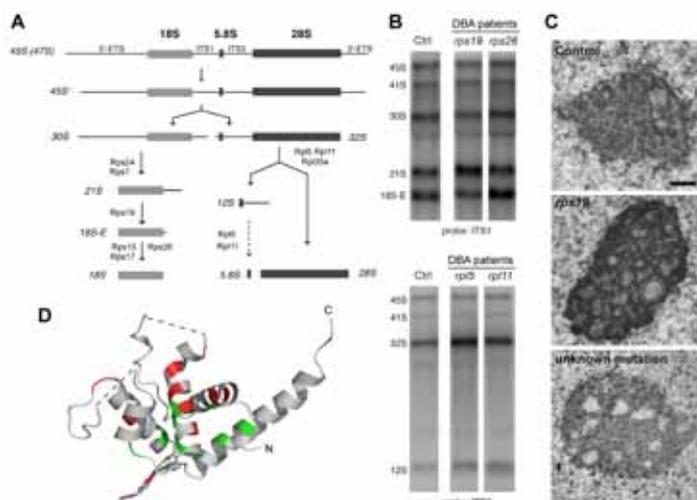
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An unexpected link between erythrocytes and ribosomes

Diamond-Blackfan anemia (DBA) is a rare disease characterized by a deficiency in red cell production, usually appearing within the first weeks after birth. This leads to a potentially fatal anemia and is often associated with developmental anomalies with a variable penetrance. This disease requires, for most patients, a permanent treatment with steroids or regular blood transfusion. In 1999, heterozygous mutations in the gene encoding the ribosomal protein RPS19 were detected in 25% of the DBA patients. This puzzling link between ribosomes and erythropoiesis was the focus of this project.

Combining crystals, yeast, and red blood cells

The impact of DBA mutations on the function of RPS19 was studied by determining the atomic structure of RPS19 using X-Ray crystallography. This structure revealed two classes of mutations, affecting either the stability of RPS19 or its capacity to interact with nascent ribosomal particles (see figure), causing in every case a defect in ribosome synthesis due to RPS19 haploinsufficiency. These data on RPS19 structure were confirmed with functional experiments in human cell lines as well as in yeast *Saccharomyces cerevisiae*, which is an excellent model to study ribosome assembly. In parallel, we engaged into a collaboration with Dr Hanna Gazda at the Children Hospital Boston, which resulted in the identification and characterization of new genes mutated in DBA, all encoding ribosomal proteins necessary for pre-rRNA maturation (see figure). Activation of stress pathways in response to ribosome synthesis defects appears to be central to DBA pathophysiology.



Involvement of ribosomal proteins in DBA

(A) Simplified view of pre-ribosomal RNA (pre-rRNA) processing. The ribosomal proteins mutated in DBA are involved at various steps of the maturation pathway. (B) Pre-rRNA maturation is affected in lymphoblastoid cells from DBA patients as shown by accumulation of some pre-rRNAs. These pre-rRNA patterns mirror knockdown of the corresponding ribosomal proteins with siRNAs (not shown). (C) Electron microscopy shows abnormal nucleoli in a patient with a mutation in RPS19 and in a patient harboring an unknown mutation. (D) Two classes of mutations emerge from RPS19 atomic structure: some affect the folding and the stability of the protein (green), whereas others change the capacity of the protein to interact with ribosomal RNA (red), which prevents incorporation into nascent ribosomal particles.

A new class of rare diseases

Our work establishes that DBA is a disease linked to the alteration of the ribosome production process. During the course of this project, several other genetic diseases have been associated with such defects, leading to the definition of a new class of diseases (ribosomopathies) for which DBA is a central model. We are currently trying to define simple protocols to detect anomalies in ribosome production and to develop novel tools for DBA diagnosis. In addition, the finding of new genes mutated in DBA allows the identification in French patients of the mutations linked to the disease.

References

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