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Mitochondrial Pathways Affected by Genetic Defects in Congenital SAS

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Introduction

A category of inherited and acquired bone marrow conditions known as sideroblastic anemias (SAs) are characterised by pathological iron accumulation in the mitochondria of erythroid precursors. The abnormal, iron-rich mitochondria that give rise to the ring (or ringed) sideroblast, a morphological trait unique to SAs, appear to encircle erythroblast nuclei. Like most haematological disorders, the molecular genetic basis of the SAs was first identified in the 1940s,4,5 and it was formalised as a class of anaemia in the 1960s,6 riding the tide of technological development. With the development of positional cloning during the past twenty years.

Description

Genome-wide next-generation sequencing and descendant mapping linkage analyses were used independently to identify TRNT1 mutations as the genetic changes that cause SIFD. The TRNT1 gene (EC 2.7.7.25), which codes for an important enzyme that catalyses the attachment of the CCA terminal to the 39 ends of transfer RNA (tRNA) precursors, was found to have germline point mutations using both approaches. Mature cytosolic and mitochondrial tRNA aminoacylation and quality control, as well as the stress response, are fundamentally dependent on this activity. Depending on the original function(s) of the mutant genes, inherited SAs have a variety of symptoms, but they are always united by the presence of ringed sideroblasts in the bone marrow aspirate.

Electron microscopy has shown that the latter are erythroblasts with abnormally coarse granules of iron deposition in the mitochondria. When stained with Perls' Prussian blue, such iron-encrusted mitochondria form a distinctive "ring" around the erythroid cell nucleus. reduce the number of syndromic forms lacking a causative gene, in particular those with SIFD. Because of the large heterogeneity of SIFD expressivity, it is difficult to calculate the exact percentage of patients carrying TRNT1 mutations because many cases might be misdiagnosed for their mild phenotype. Such cases could now be identified by TRNT1 gene sequencing.

The final result of SA in both its syndromic and non-syndrome variants is iron metabolism deregulation, which results in an iron excess in the erythroblast mitochondria and elevated mitochondrial ferritin, which is in fact the defining feature of these anemias. To prevent Fenton-type reactions and iron-induced oxidative damage, mitochondrial ferritin must protect the excess iron in these organelles. The iron overload manifests as a direct result of the involvement of a gene whose product is directly related to iron or heme metabolism in a number of nonsyndromic cases (such as those caused by mutations of XLSA, SLC25A38, GLRX5, and FECH). In many situations, anaemia is the primary cause of the symptoms. However, syndromic forms, such as ABCB7, SIFD, Pearson syndrome, myopathy with lactic acidosis and SA, and thiamine-responsive megaloblastic anaemia, seem to be linked to a defect in mitochondrial/cytosolic protein translation and, more specifically, abnormal tRNA function brought on by errors in tRNA maturation/modification or even tRNA synthesis. Deletion of tRNA genes in the mitochondria.

Accordingly, TRNT1 is necessary for the maturation of tRNA, and its decreased activity, like that of other syndromic SA, is projected to have a significant impact on cell viability by reducing total protein biosynthesis and leading to a wide range of dysfunctions in patients. The iron overload manifests as a direct result of the involvement of a gene whose product is directly related to iron or heme metabolism in a number of nonsyndromic cases (such as those caused by mutations of XLSA, SLC25A38, GLRX5, and FECH). In many situations, anaemia is the primary cause of the symptoms [1-5].

Conclusion

Contrarily, syndromic forms (such as ABCB7, SIFD, Pearson syndrome, myopathy with lactic acidosis and SA, and thiamine-responsive megaloblastic anaemia) seem to be linked to a defect in mitochondrial/cytosolic protein translation, more specifically with abnormal tRNA function brought on by flaws in tRNA maturation/modification or even deletion of mitochondrial tRNA genes. The inherited conditions known as congenital sideroblastic anemias (CSAs) are caused by flaws in the biogenesis of the iron-sulfur cluster (ISC), heme, generalised mitochondrial protein synthesis, or specific mitochondrial proteins involved in oxidative phosphorylation. This is not surprising given the crucial role mitochondria play in the metabolism of iron and heme as well as in the creation of energy. Because haemoglobin in erythroid cells contains more than two thirds of the iron in the human body, this makes erythron particularly vulnerable to disruptions in the heme biosynthesis pathway.

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Conflict of Interest

The Author declares there is no conflict of interest associated with this manuscript.

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