



A mouse model of beta-thalassemia shows a liver-specific down-regulation of Abcc6 expression

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Résumé en anglais	<p>beta-Thalassemia and pseudoxanthoma elasticum (PXE) are distinct genetic disorders. Yet, a dystrophic mineralization phenotype similar to PXE has frequently been associated with beta-thalassemia or sickle cell anemia patients of Mediterranean descent. These calcifications are clinically and structurally identical to inherited PXE. As we previously excluded the presence of PXE-causing mutations in the ABCC6 gene of beta-thalassemia patients with PXE manifestations, we hypothesized that a molecular mechanism independent of gene mutations either altered the ABCC6 gene expression or disrupted the biologic properties of its product in the liver or kidneys, which are the tissues with the highest levels of expression. To test this possibility, we investigated Abcc6 synthesis in the liver and kidneys of a beta-thalassemia mouse model (Hbb(th3/+)). We found a progressive liver-specific down-regulation of the Abcc6 gene expression and protein levels by quantitative PCR, Western blotting, and immunofluorescence. The levels of Abcc6 protein decreased significantly at 6 months of age and stabilized at 10 months and older ages at approximately 25% of the wild-type protein levels. We studied the transcriptional regulation of the Abcc6 gene in wild-type and Hbb(th3/+) mice, and we identified the erythroid transcription factor NF-E2 as the main cause of the transcriptional down-regulation using transcription factor arrays and chromatin immunoprecipitation. The Hbb(th3/+) mice did not develop spontaneous calcification as seen in the Abcc6(-/-) mice probably because the Abcc6 protein decrease occurred late in life and was probably insufficient to promote mineralization in the Hbb(th3/+) mouse C57BL/6J genetic background. Nevertheless, our result suggested that a similar decrease of ABCC6 expression occurs in the liver of beta-thalassemia patients and may be responsible for their frequent PXE-like manifestations.</p>
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