A mass spectrometric approach to investigate cardiolipin metabolism in Barth syndrome
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CHAPTER 1

Introduction
X-linked cardioskeletal myopathy and neutropenia (Barth syndrome, MIM302060, BTHS) is a disorder with mitochondrial functional impairments and 3-methylglutaconic aciduria that maps to Xq28. The associated tafazzin or TAZ gene has been identified but the encoded proteins have not yet been characterized. Until recently there was no explanation for the multicomplex disorder of the respiratory chain and the often fatal course of the disease. The TAZ gene on Xq28 became associated with the disease in 1996. Even then the function of the encoded protein(s), predicted on the basis of its DNA sequence was not immediately clear. This deadlock was overcome when structural similarity was shown between a superfamily of acyltransferases involved in phospholipid metabolism, present in many eukaryotes and prokaryotes, and tafazzin. We tested the implied hypothesis by a search for phospholipid classes in fibroblasts in controls and in patients with Barth syndrome, making use of electrospray ionization mass spectrometry. This study revealed a profound deficiency of cardiolipin in all analyzed cells and tissues from patients with Barth syndrome. The significance of this finding is underscored by the fact that cardiolipin was already known from experimental studies as a structural component of the inner mitochondrial membrane, indispensable for proper functioning of the respiratory chain. The main focus of this thesis is the study of phospholipid metabolism in Barth syndrome.

Chapter 2 reviews the current state of knowledge of lipid abnormalities in Barth syndrome. Chapter 3 describes our initial investigations into phospholipid metabolism in Barth syndrome. Biosynthesis of all major phospholipid classes was found to be normal in contrast to the abnormal remodeling of cardiolipin and its biosynthetic precursor phosphatidylglycerol. In chapter 4 a new method based on HPLC-Electrospray Mass Spectrometry for cardiolipin analysis is introduced. The method is useful for the detection of tetralinoleoyl cardiolipin deficiency in platelets of Barth syndrome patients. Chapter 5 illustrates the use of the method described in chapter 4 in cultured skin fibroblasts of healthy controls, a group of patients with mitochondrial diseases other than Barth syndrome and a group of patients suffering from Barth syndrome to answer the question whether the deficiency of tetralinoleyl cardiolipin is specific for Barth syndrome. Chapter 6 describes the effect of linoleic acid supplementation on phospholipids in cultured skin fibroblasts. Chapter 7 shows the accumulation of monolysocardiolipin, one of the intermediate components in cardiolipin remodeling, in Barth syndrome. In chapters 8 and 9 a Saccharomyces cerevisiae strain, in which the yeast orthologue of the human TAZ gene has been disrupted, is characterized. Both chapters show that this yeast orthologue exhibits an abnormal cardiolipin profile and accumulation of monolysocardiolipin. Chapter 9 addresses the question whether all the 12 different splice variants of the human TAZ gene are necessary for cardiolipin metabolism. In chapter 10 some future prospects are given.