Hepatocyte FAM210A deficiency disrupts mitochondrial function and triggers juvenile steatosis with compensatory repair in adulthood

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Abstract

Mitochondrial remodeling is essential for postnatal liver maturation and metabolic homeostasis, yet the mechanisms that preserve mitochondrial integrity during development and coordinate hepatic adaptation to mitochondrial dysfunction remain incompletely understood. In this study, we identified Family with sequence similarity 210 member A (FAM210A) as a hepatocyte-enriched mitochondrial protein that plays a critical role in juvenile liver development and metabolic homeostasis. Hepatocyte-specific deletion of *Fam210a* (*Fam210a*^{HKO}) caused transient growth restriction during early postnatal development, characterized by reduced body and liver mass, hepatic steatosis, glycogen depletion, and impaired postprandial glucose homeostasis. Transcriptomic profiling revealed broad suppression of fatty acid, sterol, bile acid, and glucose metabolic pathways, accompanied by activation of cell-cycle, glutathione, and stress-responsive programs. Consistently, mitochondrial proteomic analysis demonstrated extensive remodeling of metabolic and stress-associated pathways. Mechanistically, FAM210A deficiency impaired mitochondrial function, as evidenced by reduced mitochondrial DNA content, defective oxidative phosphorylation, diminished respiratory capacity, increased lipid peroxidation, and profound abnormalities in mitochondrial ultrastructure and cristae organization. These defects were accompanied by altered OPA1 processing, with reduced long OPA1 and accumulation of short OPA1 isoforms. FAM210A physically interacted with the mitochondrial i-AAA protease YME1L, supporting a role for FAM210A in regulating mitochondrial inner-membrane remodeling and OPA1 homeostasis. Remarkably, the juvenile hepatic abnormalities were largely resolved by adulthood, with restoration of liver morphology, lipid and glycogen homeostasis, mitochondrial DNA content, OPA1 processing, and oxidative phosphorylation protein abundance. This recovery was associated with enhanced hepatocyte proliferation and mitochondrial biogenesis, consistent with an ISR-linked compensatory stress-adaptive response. Collectively, our findings identify FAM210A as a developmental safeguard of hepatocyte mitochondrial integrity and reveal a stress-adaptive regenerative program that restores mitochondrial and metabolic homeostasis following juvenile liver dysfunction.