Age-associated metabolic and epigenetic barriers during direct reprogramming of mouse fibroblasts into induced cardiomyocytes

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Heart disease is the leading cause of mortality in developed countries, and novel regenerative procedures are warranted. Direct cardiac conversion (DCC) of adult fibroblasts can create induced cardiomyocytes (iCMs) for gene and cell-based heart therapy, and in addition to holding great promise, still lacks effectiveness as metabolic and age-associated barriers remain elusive. Here, by employing MGT (Mef2c, Gata4, Tbx5) transduction of mouse embryonic fibroblasts (MEFs) and adult (dermal and cardiac) fibroblasts from animals of different ages, we provide evidence that the direct reprogramming of fibroblasts into iCMs decreases with age. Analyses of histone posttranslational modifications and ChIP-qPCR revealed age-dependent alterations in the epigenetic landscape of DCC. Moreover, DCC is accompanied by profound mitochondrial metabolic adaptations, including a lower abundance of anabolic metabolites, network remodeling, and reliance on mitochondrial respiration. In vitro metabolic modulation and dietary manipulation in vivo improve DCC efficiency and are accompanied by significant alterations in histone marks and mitochondrial homeostasis. Importantly, adult-derived iCMs exhibit increased accumulation of oxidative stress in the mitochondria and activation of mitophagy or dietary lipids; they improve DCC and revert mitochondrial oxidative damage. Our study provides evidence that metaboloepigenetics plays a direct role in cell fate transitions driving DCC, highlighting the potential use of metabolic modulation to improve cardiac regenerative strategies.

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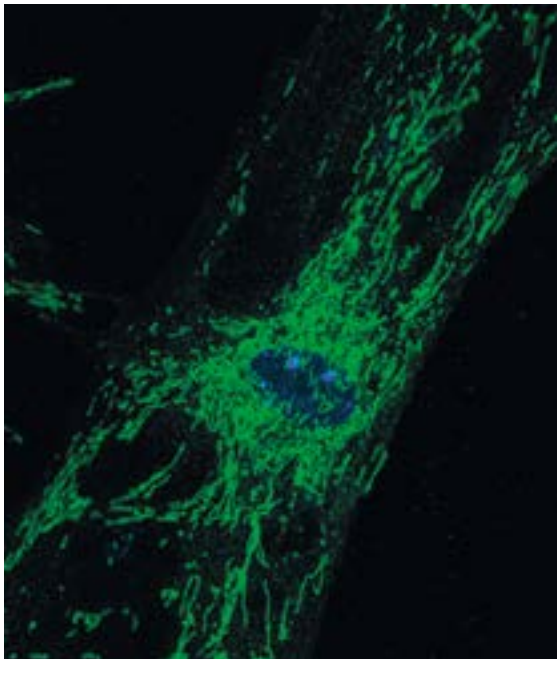

FIGURE 1
Immunofluorescence of TOM20 (green) mitochondrial protein in mouse embryonic fibroblasts transdifferentiated into iCMs, nucleus in blue.