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Modulation of Aging and Calorie Restriction Benefits by PGC-1α

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These studies attempt to link PGC-1α, a master regulator of energy metabolism, with mitochondrial decline with aging, thus possibly defining a novel therapy for age-associated disorders.

Specific Aim 1: To characterize the inability of aging PGC-1α-/- heart to benefit from calorie restriction through gene expression profiling, and to correlate these changes with specific defects in mitochondrial function. Specific Aim 2: To define a mechanism whereby PGC-1α participates in the favorable metabolic remodeling of skeletal muscle with calorie restriction.

The ability of calorie restriction (CR) to maintain a "more youthful" thinner ventricular wall was lost in the absence of PGC-1α in 20 month old mice (Fig. 1).

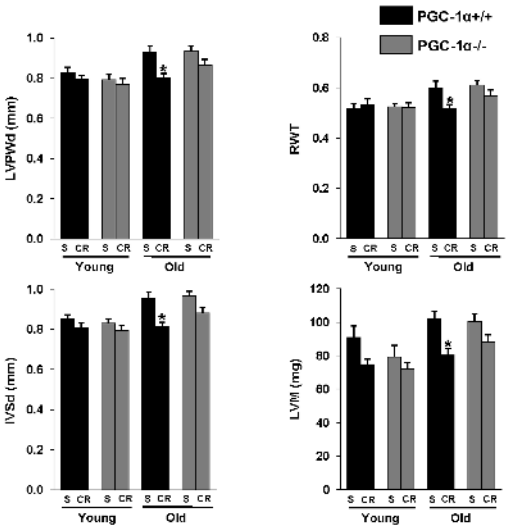
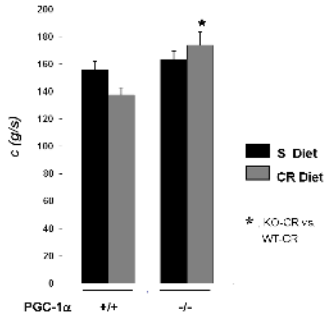


Figure 1. Echocardiographic parameters of wall thickness and left ventricular mass in young (7 month old) and old (20 month old) PGC-1α-/- vs. PGC-1α+/+ mice on either S or CR diets. LVPWd, left ventricular posterior wall thickness in diastole (mm); IVSd, interventricular septal thickness in diastole (mm); RWT, relative wall thickness (LVPWd+IVSd/LVIDd); LVM, left ventricular mass (mg). *, CR vs. S, same genotype.



Consistent with an impaired response to CR, a measure of diastolic performance known as the viscoelastic parameter Ec, which is known to be reduced (i.e., a favorable change) with human calorie restriction, was higher in calorie restricted PGC-1α-/- mice relative to CR wild-type mice at 20 months of age (Fig 2).

Figure 2. The viscoelastic parameter *c* (or Ec), inversely related to diastolic function, as assessed by echocardiographic determination of transmitral inflow waves in 20 month old PGC-1α+/+ (WT) and PGC-1α-/- (KO) mice on standard (S) and calorie restricted (CR) diets.

In an effort to correlate alterations in mitochondrial function with the observed changes in cardiac morphology and diastolic function, mitochondrial function assays measuring both oxygen (O) consumption and the efficiency of ATP production (ATP/O) were performed for both heart and soleus (Fig. 3). These studies demonstrated that loss of PGC-1α in calorie restricted animals results in marked mitochondrial energetic inefficiency – implicating PGC-1α as an essential effector of CR benefits afforded by mitochondrial remodeling or turnover.

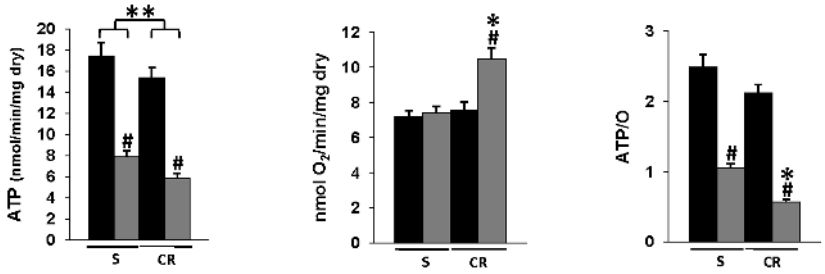


Figure 3. Maximal (State 3) ATP synthesis rates, oxygen consumption, and efficiency of ATP synthesis (ATP/O) in saponin-permeabilized soleus fibers from 2 year old PGC-1α-/- (grey bars) vs. PGC-1α+/+ (black bars) mice on S or CR diets. Studies were performed in the presence of succinate as substrate, with similar data generated from cardiac left ventricle. #, KO vs. WT, same diet; *, CR vs. S, same genotype; **, all CR vs. all S. (n=28).

Specific Aim 3: To compare mouse and human muscle gene expression data in order to define common functional gene pathways associated with youth, calorie restriction, PGC-1α deficiency, and aging.

We have harvested all 2 year old mouse heart and skeletal muscle samples needed for gene array analysis and are completing RNA isolation prior to sample submission to the Siteman Cancer Center Gene Chip Facility. The impact of calorie restriction on human muscle gene expression profiles is being assessed in skeletal muscle from control and calorie restricted humans in collaboration with ongoing studies of Dr. Luigi Fontana and Dr. John Holloszy. We are interested in the similarities of

CR effects across species, and will be very interested in mitochondria-related pathways, especially those that regulate cardiolipin, a key mitochondrial membrane lipid necessary for mitochondrial efficiency. Our preliminary lipidomic data (Fig 4) suggests that cardiolipin may be inappropriately reduced and oxidatively damaged in hearts of calorie restricted PGC-1α-/- mice.

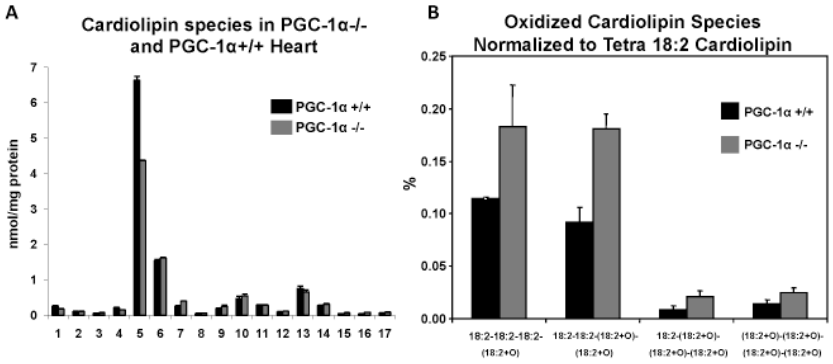


Figure 4. Preliminary lipidomic analysis by mass spectrometry of cardiolipin species in heart from 2 year old PGC-1α-/- vs. PGC-1α+/+ mice on CR diets. The dominant species of cardiolipin (tetra 18:2, denoted as species 5 in "A") is reduced by 35% in hearts of PGC-1α deficient, calorie restricted mice (A) and is markedly oxidatively damaged (B).