Cell Metabolism
Response

Response to Handschin and Spiegelman

Dear Editor,

We wish to respond to the interesting points raised by Drs. Handschin and Spiegelman regarding our paper (Zechner et al., 2010). We concluded that PGC-1 coactivators are dispensable for fundamental (developmentally determined) muscle fiber-type determination in mice based on the phenotype of muscle PGC-1α/β-deficient mice (PGC-$1\alpha^{-/-}\beta^{f/f/MLC\text{-}Cre}$) (Zechner et al., 2010). Handschin and Spiegelman suggest that this model, which includes generalized PGC-1α deficiency, precludes such conclusions given that an independent muscle-specific PGC-1α knockout (MKO) line exhibits reduced oxidative muscle fiber proportions (Handschin et al., 2007). The following points should be considered relevant to this concern. First, in contrast to the phenotype of the PGC-$1\alpha^{-/-}\beta^{f/f/MLC\text{-}Cre}$ mice, the MKO mice have significant chronic muscle damage, which is known to cause a reduction in oxidative fibers in wild-type animals. Second, compared to other muscles, Handschin et al. did not find a significant reduction in type 1 fiber staining in soleus of the MKO mice, a muscle which is enriched in PGC-1α and contains a high proportion of type 1 fibers. Third, others have identified independent factors, such as MEF2c, that are required for fundamental muscle fiber-type determination (Potthoff et al., 2007), consistent with our conclusions (Zechner et al., 2010).

We agree that the use of a generalized PGC-1α KO model could result in confounding secondary (in this case compensatory) effects driven by PGC-1α deficiency in nonmuscle tissues. However, even if such independent pathways are activated, our conclusion that fiber-type determination can occur via PGC-1-independent pathways remains valid. Moreover, we have recently shown that type 1 fiber proportions are not diminished in cultured skeletal myotubes generated from muscle satellite cells isolated from PGC-$1\alpha^{-/-}\beta^{f/f/MLC\text{-}Cre}$ mice (data not shown), consistent with our in vivo data (Zechner et al., 2010). Taken together, we maintain our conclusion that whereas PGC-1 coactivators may be sufficient to drive physiological (e.g., exercise) muscle fiber-type shifts, as suggested by the work of the Spiegelman group, they are not required for fundamental fiber-type determination.

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