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Dear Editor,

we would like to offer a comment and alternative viewpoint regarding the recent manuscript by Zechner et al. (Zechner et al., 2010), which described the phenotypic outcome in skeletal muscle resulting from genetic loss-of-function for both PGC-1α and PGC-1β. Zechner and coworkers specifically ablated PGC-1β in skeletal muscle, either alone or in a global PGC-1α knockout background. Based on the findings from these experiments, Zechner and colleagues concluded that the PGC-1 coactivators are dispensable for muscle fiber-type determination and are not involved in the development of insulin resistance. While we have no issues at all with their data, we think that this conclusion may not be justified based on the limitations of the experimental system and in light of previously published work. We have previously demonstrated that mice with a global PGC-1α knockout do not exhibit a change in the fiber-type distribution in skeletal muscle (Arany et al., 2005), exactly as Zechner et al. did in the present manuscript; however, in contrast, skeletal muscle-specific knockout animals for PGC-1α have a significant shift from oxidative towards glycolytic muscle fibers (Handschin et al., 2007). We have noted this discrepancy between the global and muscle-selective KOs and have speculated that it most likely originates from the very complex phenotype of the global knockout mice (Lin et al., 2004). For example, in addition to the difference in fiber-type distribution, global PGC-1α knockout animals have a constitutively activated AMPK in muscle and exhibit a different response to endurance exercise training, compared to mice with a muscle-specific ablation of PGC-1α (Chinsomboon et al., 2009; Lin et al., 2004). Similar discrepancies between global and tissue-specific PGC-1α ablation have been observed in other organs, including the regulation of hepatic gluconeogenesis. Therefore, in the experimental context of a global PGC-1α knockout background, any conclusions about the role of PGC-1α in skeletal muscle fiber-type regulation could be problematic and are likely to be confounded. Of course, other observations, such as the unchanged insulin sensitivity in the single and double knockout mouse seen by Kelly's group, could also be affected by the previously reported major metabolic differences in whole body PGC-1α knockouts vs. controls. The whole body KOs are characterized by elevated metabolic rates and hyperactivity, in contrast to the hypoactivity observed in the PGC-1α muscle-specific knockout mice. The latter also have altered pancreatic β cell function, which is not seen in that form the full body KOs. Finally, and perhaps most importantly, both PGC-1α and PGC-1β expression

levels are reduced specifically in the skeletal muscle of type 2 diabetic patients. Thus, there is ample published data to indicate that caution should be exercised in drawing conclusions from mice with a full-body KO for PGC1α to model the human patients. Conclusive studies about the physiological function and pathophysiological dysregulation of the two PGC-1 coactivators PGC-1α and PGC-1β in skeletal muscle will have to be performed in tissue-specific models.

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