# Phb1:Phb2 heterodimers in the mitochondria—beyond functional interdependence

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Li *et al.* (1) showed that *in vivo* deletion of prohibitin-2 (Phb2) in hepatocytes (Hep-Phb2$^{-/-}$) leads to impaired gluconeogenesis, reduced food intake, severe hypoglycemia, and, subsequently, poor survival. Phb2 and its homologous protein Phb1 form heterodimers in the mitochondria and are functionally interdependent (1–3). Consequently, the knockdown of either member leads to a parallel loss of the other member (1–4). Thus, it remains unclear whether or not Phb1 and Phb2 have protein-specific functions in the mitochondria.

Of note, the hepatocyte-specific Phb1 knockout (Hep-Phb1$^{-/-}$) mouse model has been developed (4). Unfortunately, Li *et al.* did not acknowledge a single article published on the Hep-Phb1$^{-/-}$ mouse model (4–6). Similar to the Hep-Phb2$^{-/-}$ mice, the Hep-Phb1$^{-/-}$ mice display a parallel reduction in the levels of heterodimeric partners in hepatocytes and decreased body weight (1, 4). However, the major liver-specific phenotypes of the Hep-Phb1$^{-/-}$ mice and the Hep-Phb2$^{-/-}$ mice are largely different, with distinctions like increased liver weight and the development of hepatocellular carcinoma in the former and reduced liver weight and severe hypoglycemia in the latter (1, 4). Most importantly, the Hep-Phb1$^{-/-}$ mice survive much longer than the Hep-Phb2$^{-/-}$ mice (1, 4) and other, cell type–specific knockout mouse models of Phb2 (2, 3). There could be a number of potential explanations for these differences; however, given that Phb1 and Phb2 function as the same heterodimeric complex in mitochondria, it is intriguing that they have such different phenotypes. It appears that the mitochondrial biology of Phb1 and Phb2 is more complex than simple interdependence. The development of the Hep-Phb2$^{-/-}$ mouse model along with the preexisting Hep-Phb1$^{-/-}$ mouse model provided an opportunity to initiate discussion around this stimulating question, which is completely missed by Li *et al.* (1).

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