Reply to Mishra: Prohibitin heterodimers—a complex time dependence for carcinogenesis

DOI 10.1074/jbc.RL119.010819

Juliette Martin-Levilain[‡§], **Lingzi Li**[‡§], **and Pierre Maechler**[‡§1]

From the [‡]*Department of Cell Physiology and Metabolism and the* [§]*Faculty Diabetes Centre, University of Geneva Medical Centre, 1206 Geneva, Switzerland*

Edited by Jeffrey E. Pessin

Dr. Mishra (1) points to an interesting aspect of Phb1/Phb2 interdependence and tumor formation. Constitutive liver-specific Phb1-KO mice develop hepatocellular carcinoma (2). Through a putative mirror effect, Dr. Mishra extrapolates on the phenotype of our Hep-*Phb2*$^{-/-}$ mice (3) that should supposedly be similar to liver-specific Phb1-KO (2), according to Phb1/Phb2 interdependence. While both models are liver-specific, our Phb2-KO is time-specific (*Phb2*$^{fl/fl}$;Alb-*Cre*-ER^{T2}), not constitutive. Specifically, we induced the KO in adult mice (8 weeks old), avoiding the absence of liver prohibitins at the embryonic and developmental stages.

Although unpublished, we also generated constitutive liver-specific Phb2-KO (*Phb2*$^{fl/fl}$;Alb-*Cre*). In such a case, we likewise observed hepatocellular carcinoma with visible nodules on livers of 11-week-old Phb2-KO mice (see Fig. 1), compared with a similar observation in constitutive Phb1-KO by the age of 20 weeks (2). Deletion of liver Phb2 postponed at the adult stage rapidly alters the health status of Hep-*Phb2*$^{-/-}$ mice with severe hypoglycemia (3). Genetically induced cancer development in mice usually takes months (4). Acute deletion of Phb2 over a 2–3-week period is probably too short for carcinogenesis to manifest, and hence none of the livers collected from late onset Hep-*Phb2*$^{-/-}$ displayed visible nodules (3).

In conclusion, similar constitutive KO models (Phb1-KO/low-Phb2 *versus* Phb2-KO/low-Phb1) exhibit similar phenotypes. So why does the abrogation of liver prohibitins at the embryonic stage not induce major metabolic defects? Compensatory mechanisms might be progressively induced, in particular over a period where the glycemia does not rely on hepatic glucose production. These fascinating prohibitin-dependent adaptations certainly deserve further investigation.

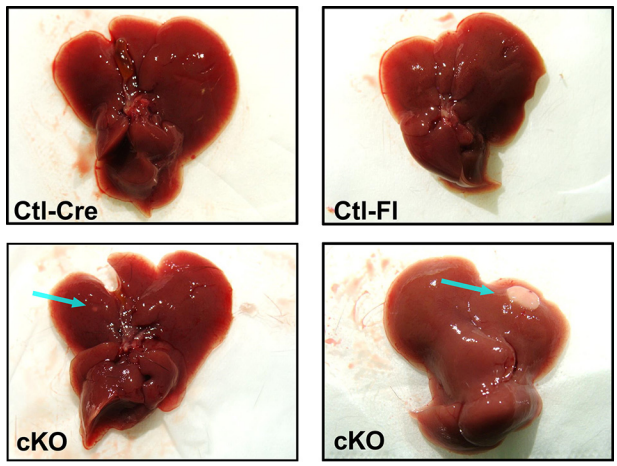

Figure 1. Representative macroscopic pictures of livers. Livers were collected at 11 weeks of age from control Cre (*Ctl-Cre*) (*Phb2*$^{+/+}$;Alb-*Cre*), control floxed (*Ctl-Fl*) (*Phb2*$^{fl/fl}$), and constitutive liver-specific knockout (*cKO*) (*Phb2*$^{fl/fl}$;Alb-*Cre*) mice. *Blue arrows* indicate nodules on representative livers ($n = 4–5$).

The authors declare that they have no conflicts of interest with the contents of this article.

[1] To whom correspondence may be addressed. E-mail: Pierre.Maechler@unige.ch.

References

1. Mishra, S. (2019) Phb1:Phb2 heterodimers in the mitochondria: Beyond functional interdependence. *J. Biol. Chem.* **294,** 14836
2. Ko, K. S., Tomasi, M. L., Iglesias-Ara, A., French, B. A., French, S. W., Ramani, K., Lozano, J. J., Oh, P., He, L., Stiles, B. L., Li, T. W., Yang, H., Martínez-Chantar, M. L., Mato, J. M., and Lu, S. C. (2010) Liver-specific deletion of prohibitin 1 results in spontaneous liver injury, fibrosis, and hepatocellular carcinoma in mice. *Hepatology* **52,** 2096–2108 CrossRef Medline
3. Li, L., Martin-Levilain, J., Jiménez-Sánchez, C., Karaca, M., Foti, M., Martinou, J. C., and Maechler, P. (2019) *In vivo* stabilization of OPA1 in hepatocytes potentiates mitochondrial respiration and gluconeogenesis in a prohibitin-dependent way. *J. Biol. Chem.* **294,** 12581–12598 CrossRef Medline
4. Heindryckx, F., Colle, I., and Van Vlierberghe, H. (2009) Experimental mouse models for hepatocellular carcinoma research. *Int. J. Exp. Pathol.* **90,** 367–386 CrossRef Medline