

**Title:** Species differences in glycerol-3-phosphate metabolism reveals trade-offs between metabolic adaptations and cell proliferation.

**Authors:**

Kateryna Gaertner, Mügen Terzioglu, Craig Michell, Riikka Tapanainen, Jaakko Pohjoismäki, Eric Dufour and [Sina Saari](#)

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**Abstract**

The temperate climate-adapted brown hare (*Lepus europaeus*) and the cold-adapted mountain hare (*Lepus timidus*) are closely related and interfertile species. We investigated the properties of skin fibroblasts collected from sympatric hare populations in Finland as a proxy for studying species divergence. Hare skin fibroblasts display distinct gene expression profiles related to fundamental cellular processes which indicates important metabolic divergence between the two species. Through targeted metabolomics and metabolite tracing, we identified species-specific variations in glycerol 3-phosphate (G3P) metabolism. G3P is a key metabolite of the G3P shuttle, which transfers reducing equivalents from cytosolic NADH to the mitochondrial electron transport chain (ETC), consequently regulating glycolysis, lipid metabolism, and mitochondrial bioenergetics. Alterations in G3P metabolism have been implicated in multiple human pathologies including cancer and diabetes. We observed that mountain hare mitochondria exhibit elevated G3P shuttle activity, alongside increased membrane potential and decreased mitochondrial temperature. Silencing mitochondrial G3P dehydrogenase (GPD2), which couples the conversion of G3P to the ETC, uncovered its species-specific role in controlling mitochondrial membrane potential and highlighted its involvement in skin fibroblast thermogenesis. Unexpectedly, GPD2 silencing enhanced wound healing and cell proliferation rates in a species-specific manner. Our study underscores the pivotal role of the G3P shuttle in mediating physiological, bioenergetic, and metabolic divergence between these hare species.