2k brief Neurodegenerative

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High-resolution respirometry and neurodegenerative disease

PNAS

PARL deficiency in mouse causes Complex III defects, coenzyme Q depletion, and Leigh-like syndrome.

Spinazzi M[1,2], Radaelli E[3], Horré K[4,2], Arranz AM[4,2], Gounko NV[4,2,5], Agostinis P[6], Maia TM[7,8,9], Impens F[7,8,9], Morais VA[10], Lopez-Lluch G[11,12], Serneels L[4,2], Navas P[11,12], De Strooper B[1,2,13].

PARL, a protease of the mitochondrial inner membrane, is key for Parkinson's disease and diabetes but plays an unclear physiological role

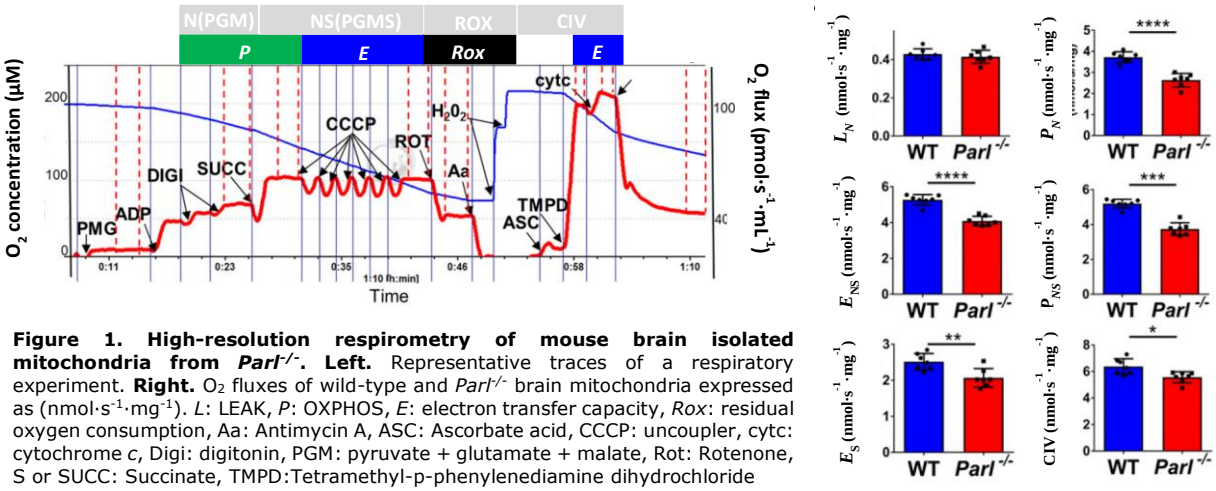

Figure 1. High-resolution respirometry of mouse brain isolated mitochondria from *Parl*$^{-/-}$. Left. Representative traces of a respiratory experiment. **Right.** O_2 fluxes of wild-type and *Parl*$^{-/-}$ brain mitochondria expressed as (nmol·s^{-1}·mg^{-1}). *L*: LEAK, *P*: OXPHOS, *E*: electron transfer capacity, *Rox*: residual oxygen consumption, Aa: Antimycin A, ASC: Ascorbate acid, CCCP: uncoupler, cytc: cytochrome *c*, Digi: digitonin, PGM: pyruvate + glutamate + malate, Rot: Rotenone, S or SUCC: Succinate, TMPD:Tetramethyl-p-phenylenediamine dihydrochloride

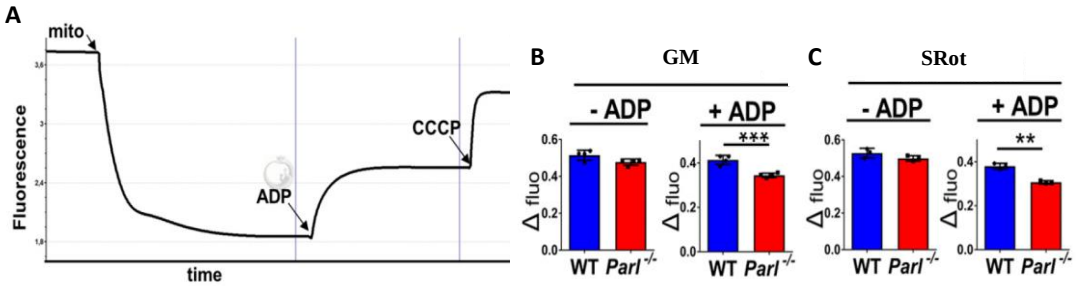

Figure 2. Mitochondrial membrane potential in *Parl*$^{-/-}$ mouse brain isolated. A. Representative trace of a typical evaluation of membrane potential by Safranin O using High-Resolution FluoRespirometry. **B.** and **C.** Bars represent $\Delta\psi_m$ of wild-type and *Parl*$^{-/-}$ isolated brain mitochondria with NADH- or S-linked substrates. GM: glutamate + malate, SRot: succinate + rotenone.

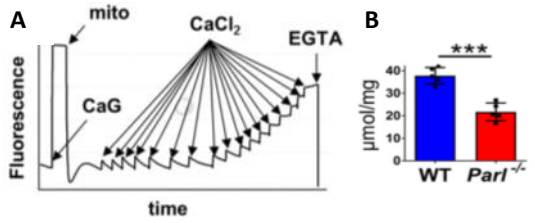

Figure 3. Ca^{2+}-retaining capacity of *Parl*$^{-/-}$ isolated mouse brain mitochondria respiring on NADH-linked pathway. A. Representative trace of High-Resolution FluoRespirometry experiment using Calcium Green. **B.** Assessment of the maximal amount of exogenous Ca^{2+} retained by wild-type and *Parl*$^{-/-}$ brain mitochondria before observing Ca^{2+} efflux. CaG: calcium Green, $CaCl_2$: calcium chloride.

Isolated brain mitochondria from *Parl*$^{-/-}$ mice showed a decreased Ca^{2+} retention capacity and an impairment in ET and OXPHOS states linked to N- and NS-pathways

PARL plays an essential role in the nervous system being required for the maintenance of mitochondrial structure and function at level of complex III, coenzyme Q and Ca^{2+} metabolism

Reference: Spinazzi M, Radaelli E, Horré K, Arranz AM, Gounko NV, Agostinis P, Maia TM, Impens F, Morais VA, Lopez Lluch G, Serneels L, Navas P, De Strooper B (2019) PARL deficiency in mouse causes Complex III defects, coenzyme Q depletion, and Leigh-like syndrome. Proc Natl Acad Sci U S A 116:277-86.