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Controversies on the potential therapeutic use of rapamycin for treating a lysosomal cholesterol storage disease

Precision medicine aims at developing tailored interventions for each patient based on their biology. This is particularly relevant for lysosomal storage disorders (LSDs), such as Niemann-Pick type C (NPC), where disease symptoms are highly heterogeneous among patients and paradoxically one-size-fits-all therapeutic approaches are usually proposed. Under this logic, the use of rapamycin has been explored in cell-based models of NPC disease showing contradictory results. On one hand, induction of autophagy with rapamycin increased the levels of cholesterol buildup in human skin NPC cells and its inhibition decreased cholesterol accumulation, indicating that autophagy is an important source of stored cholesterol in NPC lysosomes [1]. In addition, NPC-induced mitochondrial fragmentation can be rescued by the autophagy inhibitor 3-methyladenine in human NPC neurons [2], suggesting that inhibition of autophagy could be a therapeutic option for NPC. On the other hand, stimulating autophagy with rapamycin restored the autophagic flux in human NPC iPSC-derived hepatic and neuronal cells, leading to increased cellular viability [3], suggesting that promotion of autophagy may be a strategy for treating NPC disease. Can both lines of evidence be correct?

To test the therapeutic outcomes of rapamycin for NPC disease progression, male *Npc1*$^{-/-}$ mice from C57BL6/J (C57) and FVB/NJ (FVB) genetic backgrounds, which have been previously generated [4,5] were treated starting from postnatal day 20. Average lifespan of PBS-treated FVB-NPC mice is ~75-days, while C57-NPC survive ~30 days. Rapamycin, which was prepared as previously described [6], led to an amazing 100% increase in lifespan in the C57 background ($p = 0.00592$); however it was toxic for the FVB-NPC mice, reducing their lifespans ($p = 0.00265$) (Fig. 1).

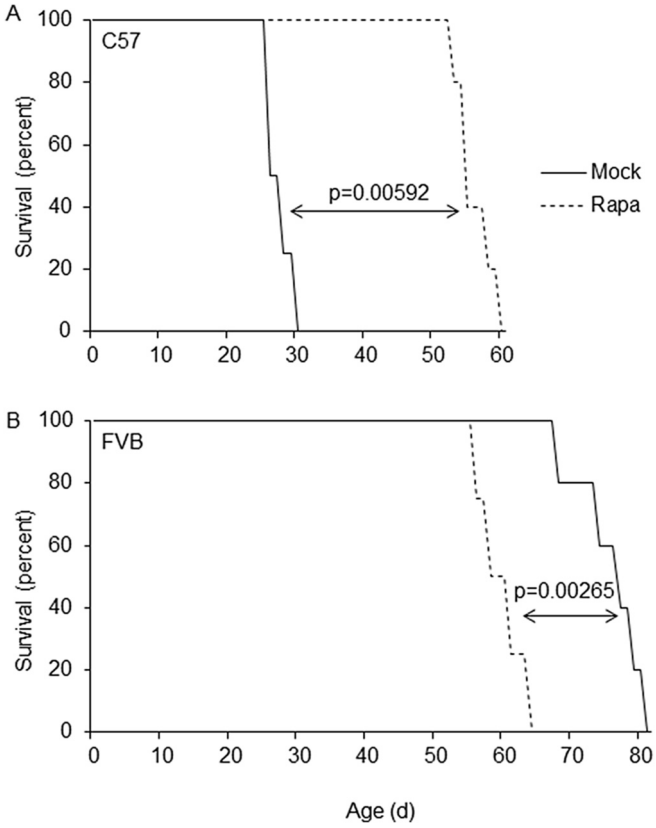

Fig. 1. Rapamycin exerts opposite effects on NPC mice depending on their genetic background. Kaplan-Meier survival curves (in days) of *Npc1*$^{-/-}$ mice from the C57 (A) and FVB (B) genetic backgrounds daily i.p. injected with Mock (solid lines) or Rapamycin (Rapa) (10 mg/kg) (dashed lines). Significant differences in survival curves were determined by Log-rank (Mantel–Cox) analyses. Values were considered statistically significantly different when $p \leq 0.05$. Animal studies are in compliance with regulations set by our Institutional Animal Care and Use Committee.

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Our paradoxical result, in addition to the contradictory published cell-based data, indicates that other factors besides loss of NPC1 function influence NPC pathophysiology and the way patients should be treated. Rapamycin, an FDA-approved drug, in addition to activate autophagy has immunosuppressive properties [7]. How rapamycin exerts its differential effects in NPC models must be further interrogated. However, extreme caution is advised at drawing conclusions on treatment of diseases like NPC based on data from a single strain [8]. We hope our study contributes to designing individualized therapies for the needs of each patient.

Conflict of interest

None.

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