NORN GROUP

Late Life Rapamycin: Still Extends Lifespan

Presented by Kush Sharma on 2/06/2022

Discussion Summary

Paper(s): Harrison, D., Strong, R., Sharp, Z. *et al.* Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 460, 392–395 (2009). https://doi.org/10.1038/nature08221

Background / Context

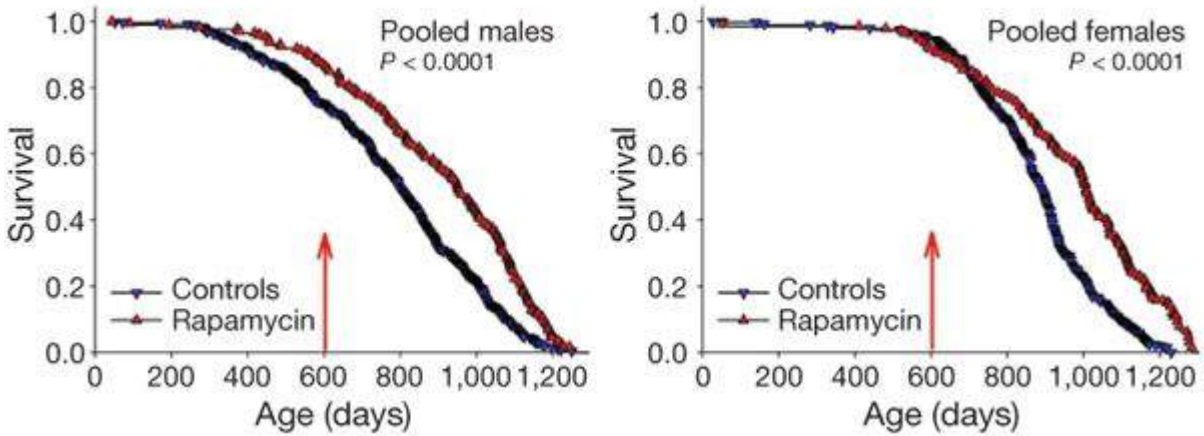
- Rapamycin is a drug that had previously been shown to extend lifespan in yeast and invertebrates
  - Rapamycin is primarily an inhibitor of mTORc1, a central metabolism regulator that senses nutrient quantities and energy availability to turn the cell either towards growth/proliferation or conversation of resources (e.g. autophagy)
  - It's hypothesised that mTORc1 inhibition is the mediating mechanism of caloric restriction's effects on lifespan; notably, late life CR does **not** extend lifespan
- The National Institute on Aging's Interventions Testing Program (NIA ITP, see previous presentation) aims to rigorously test lifespan extension effects of compounds by testing genetically heterogeneous mice across 3 different testing sites
- This paper tested rapamycin administration via diet to mice beginning at 600 days and 270 days

Overview

- This study fed mice dietary encapsulated rapamycin, starting at either 600 days or 270 days
  - Rapamycin was microencapsulated to survive the food prep process, and administered at ~2.24 mg/kg/day
  - Effectiveness was confirmed via blood concentration measurements and Western blot confirming inhibition of phosphorylation of a downstream mTORc1 target (S6K1)
- Rapamycin extends median and max lifespan of male and female mice, for both the 600 day cohort and the 270 day cohort
  - Some complications in the 600 day males…
- As far as we can tell, rapamycin did not change the causes of death in the treatment group

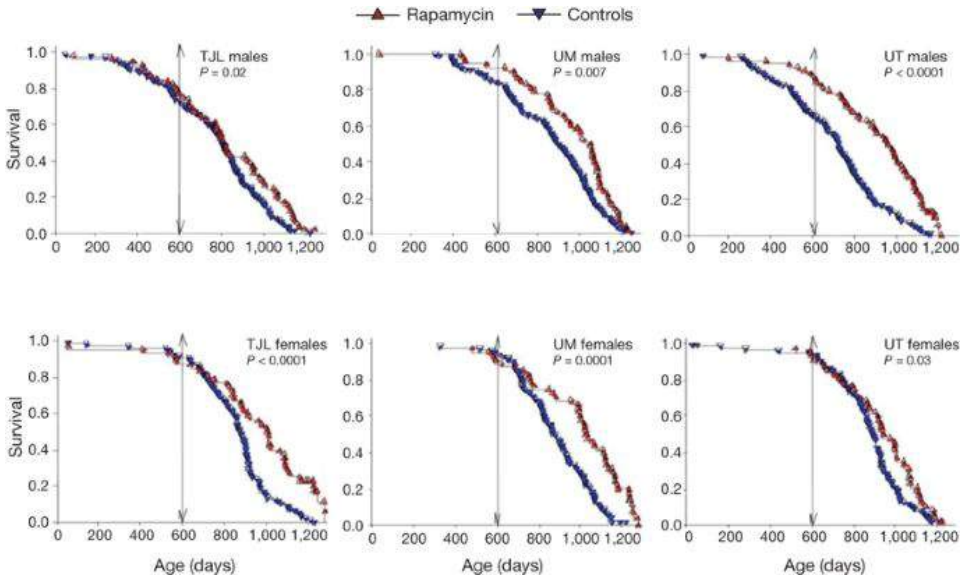
600 day cohort

- Pooled data showed significant lifespan extension for both males and females
  - 9% mean lifespan extension for males, 12% for females
  - Expressed as life expectancy at 600 days, 28% for males and 28% for females



600 day cohort cont.

- Rapamycin also extends lifespan in each of the cohorts, for all genders, but ⅔ of the male cohorts show differences in control vs. treatment lifespan *before* the start of rapamycin administration
- These two groups had differences in the chow fed, which likely accounts for *some* of the difference (all other groups had identical chow)
- So, of the unbiased data, 3 female and 1 male sites show lifespan extension



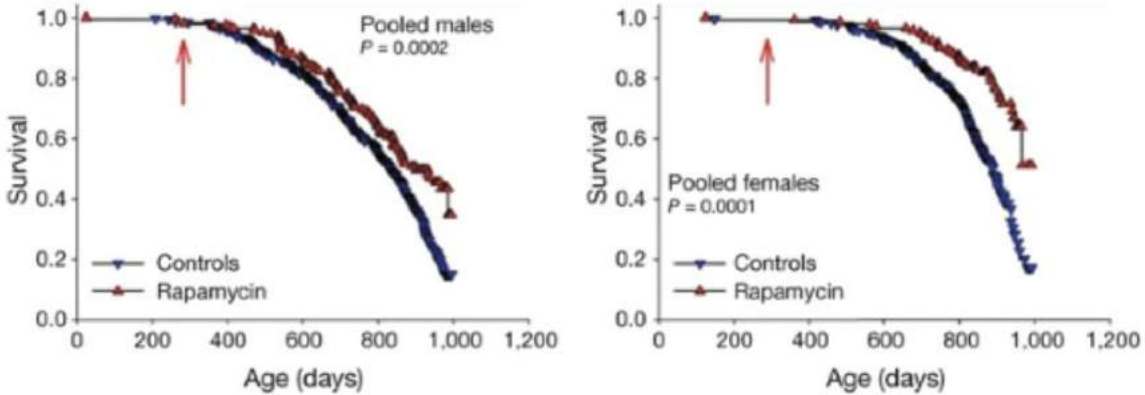
600 day cohort cont.

- Specific data if curious:

Comparison	Sites	Percentage increase
Females		
Rapamycin versus controls	All sites	14
Rapamycin versus controls	TJL	17
Rapamycin versus controls	UM	14
Rapamycin versus controls	UT	8
Males		
Rapamycin versus controls	All sites	9
Rapamycin versus controls	TJL	10
Rapamycin versus controls	UM	4
Rapamycin versus controls	UT	16

270 day cohort

- The data from the 270 day cohort was analyzed when only ~60% of the mice had died, so we don't have lifespan data, but there were stat. sig. differences in the survival curve for both genders



Conclusion

- Lifespan extension is clear (rapa works!), mechanism of extension unclear
- Clearly some sex-dependent effects, corroborated by other studies
- Effects of dosing, dosing schedule, and initiation time on lifespan left unclear
  - Other studies have shown larger lifespan increases with higher doses than this study
  - No good data on this to date
- Of course, the existence and magnitude of human effect size is unknown