

Cockayne syndrome group B protein prevents mitochondrial stress and promotes autophagy

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Cockayne syndrome

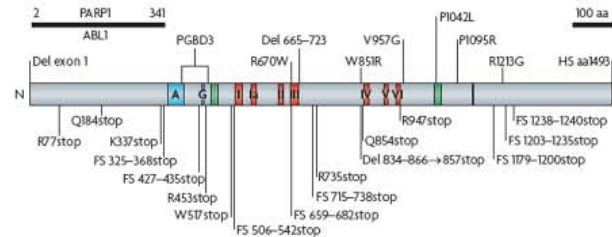
- Autosomal recessive progeria
- Rare: Estimated incidence of 2 per million births
- Clinical manifestations:
 - **Neurodegeneration**
 - **Cachectic dwarfism**
 - Cataracts, Sensorineural hearing loss, dental caries, muscle weakness
 - Photosensitivity but no cancer susceptibility
- Mutation in CSB, 80%, and CSA, 20%



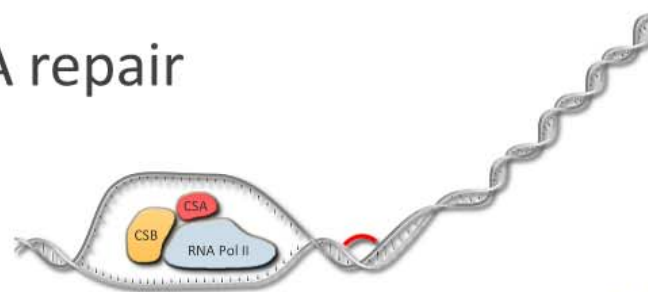
Lindenbaum et al. EJPN 2001

CSB gene

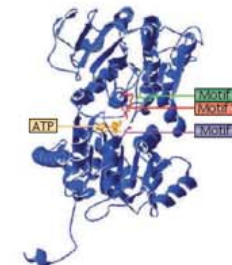
- Mutated in 80% of the Cockayne syndrome Nance and Berry, Am J Med Genet 1992



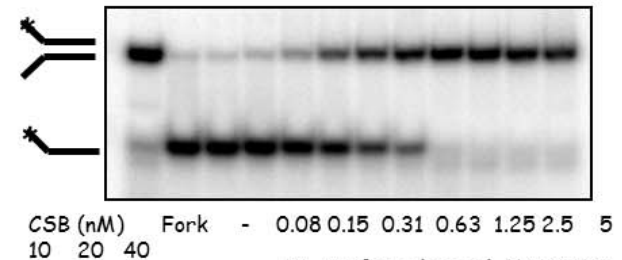
- Involved in TC-NER DNA repair



- Belongs to the SWI/SNF2 family of DNA dependent ATPases



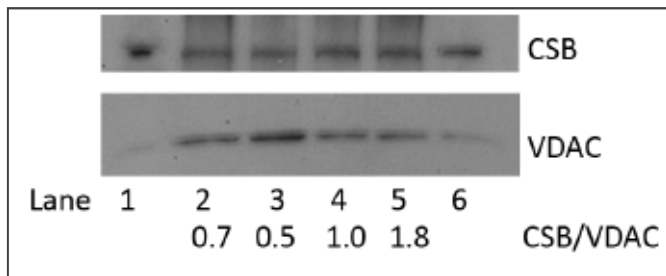
- Strand annealing but no helicase



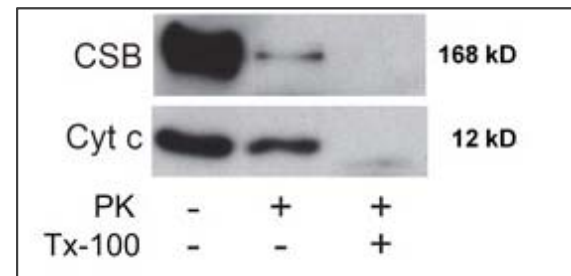
M. Muftuoglu et al. NAR 2006

Cells deficient in CSB accumulate oxidative damage

- Oxidative lesions were found to accumulate in mitochondria from cells defective in CSB
- CSB deficient cells were found to be hypersensitive to oxidative stress
- CSB localizes to the mitochondria



Aamann *et al.* FASEB 2010

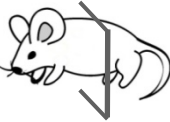


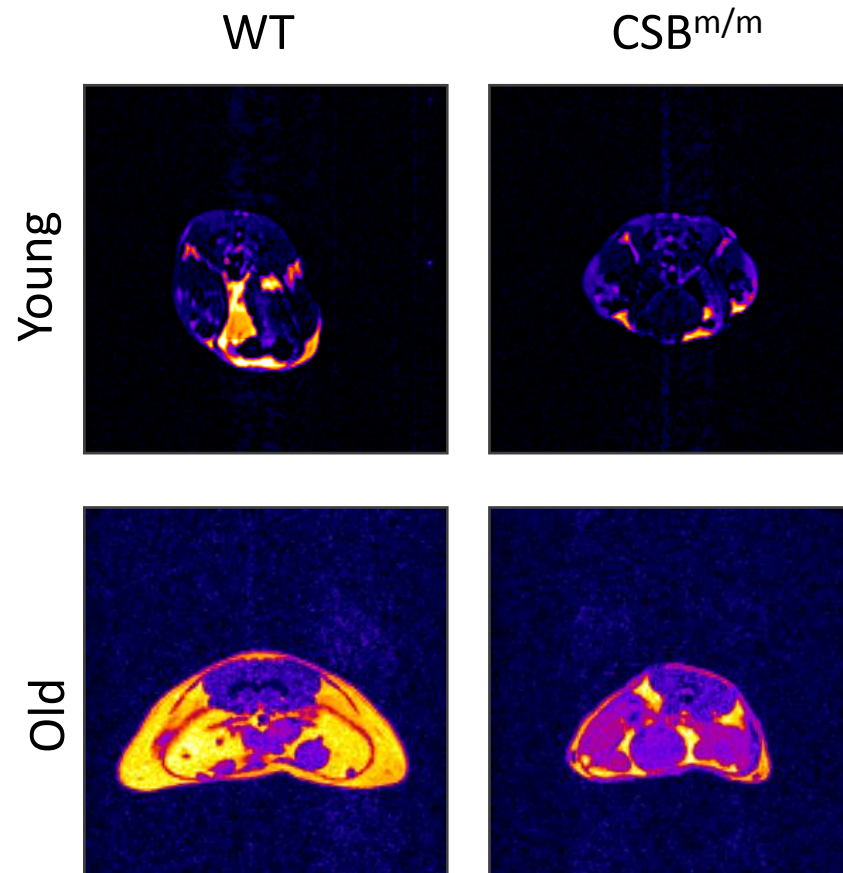
Kamenisch *et al.* JEM 2010

Hypothesis

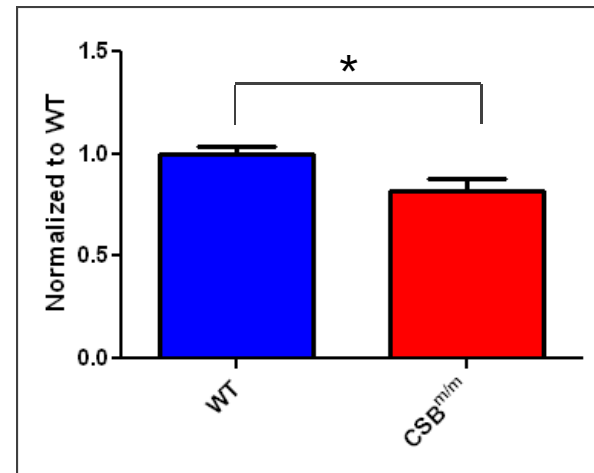
- CSB participates in mitochondrial DNA maintenance
- CSB deficiency leads to dysfunctional mitochondria, increased energy consumption and the characteristic phenotype

T1 weighted MRI scans of CSB^{m/m} mice

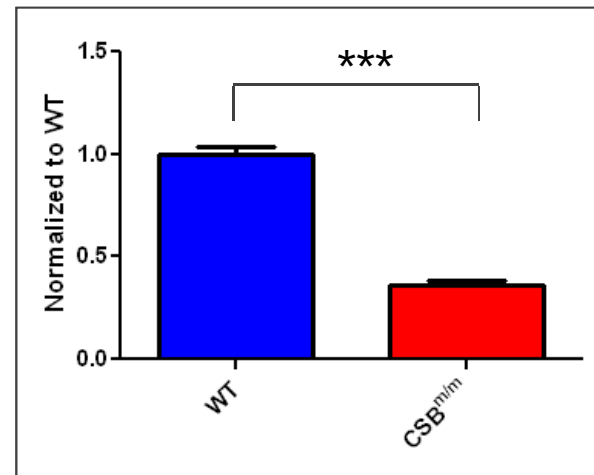
Axial scan: 



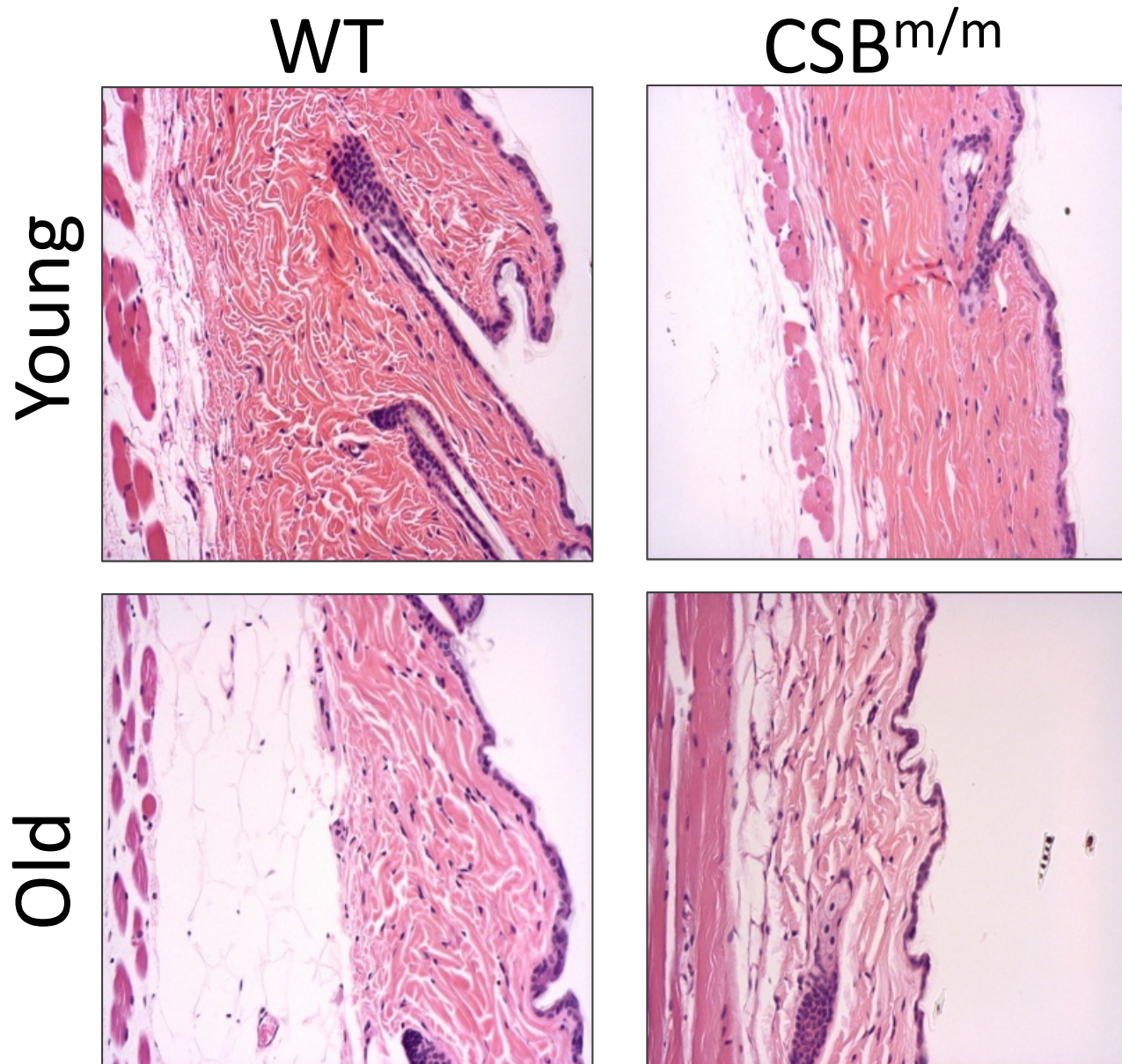
Young



Old

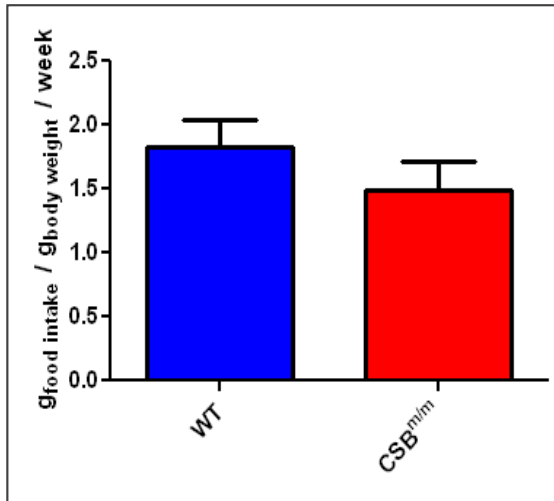


Old CSB^{m/m} mice show subcutaneous fat loss

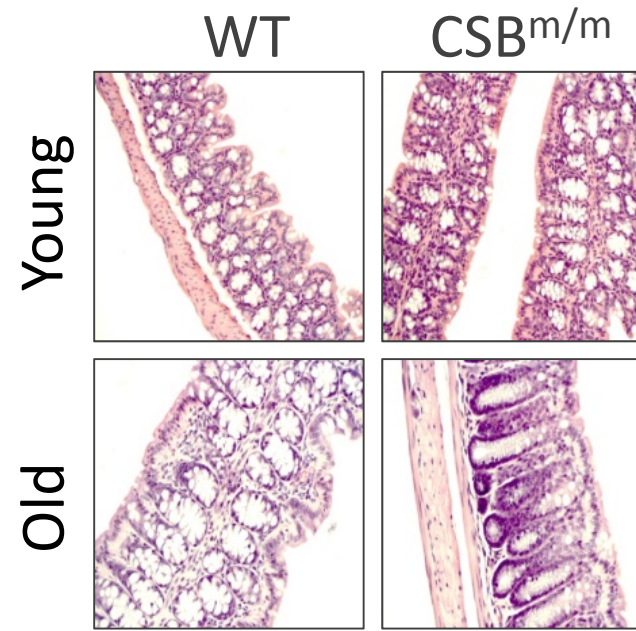
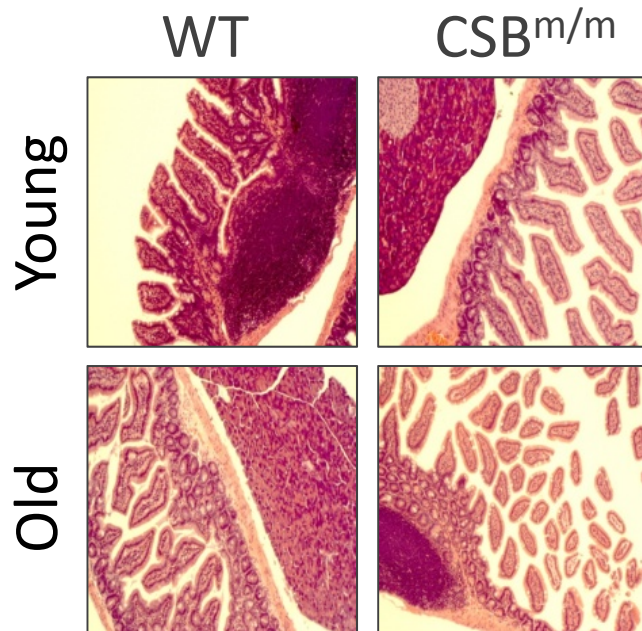
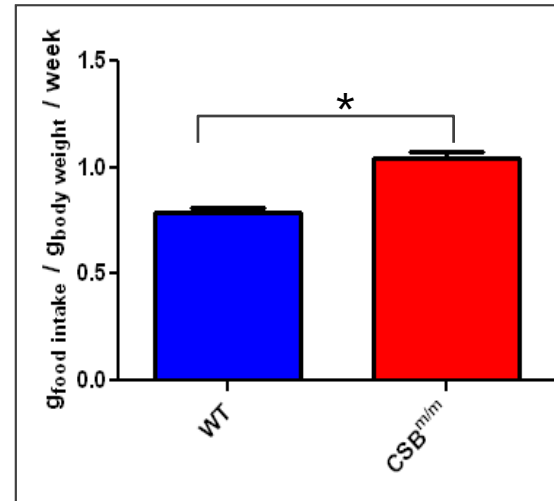


Old CSB^{m/m} mice have increased food intake

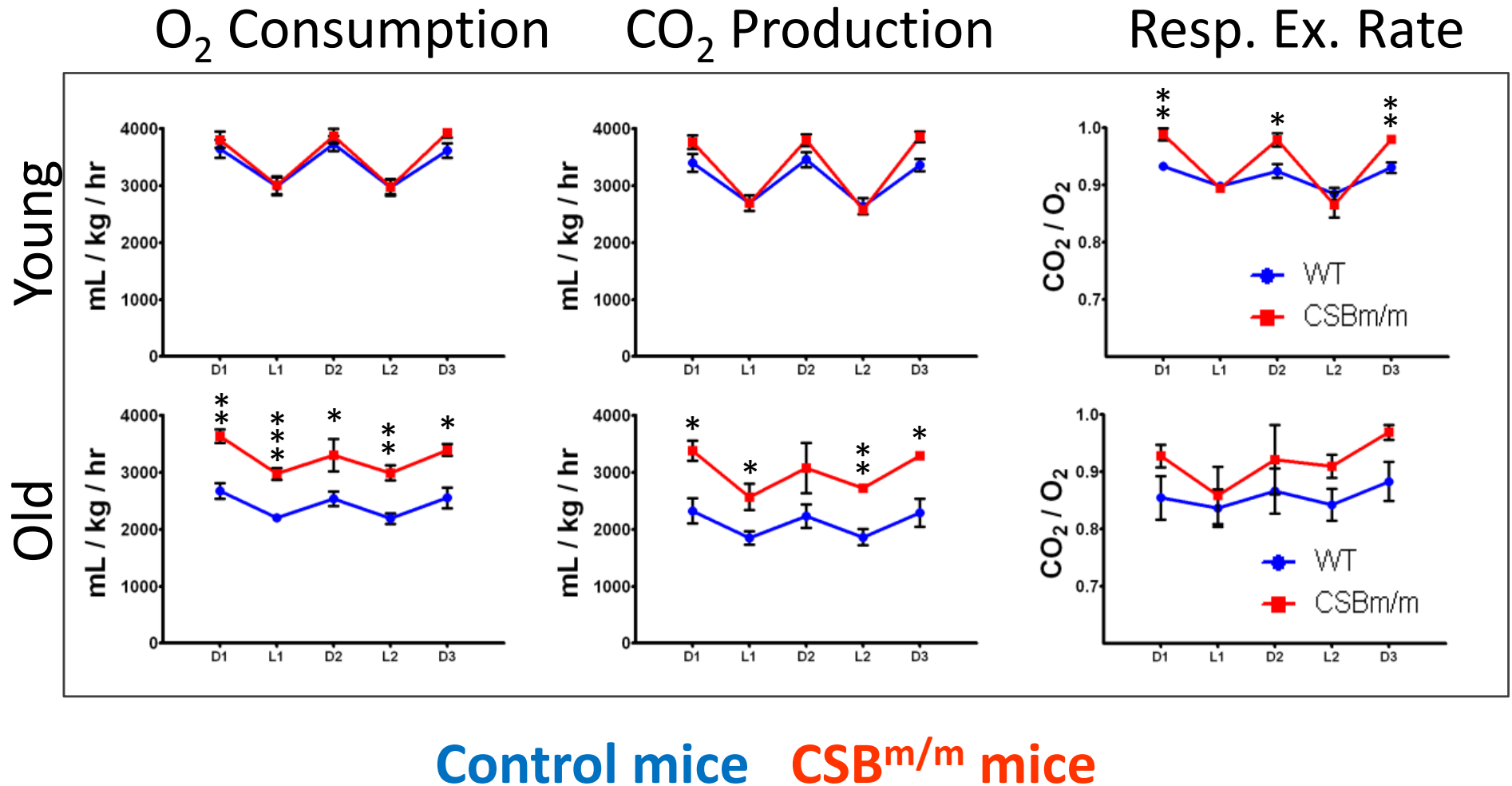
2 months



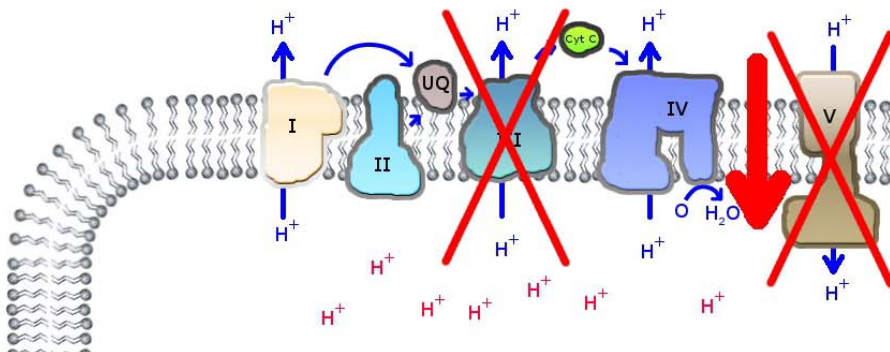
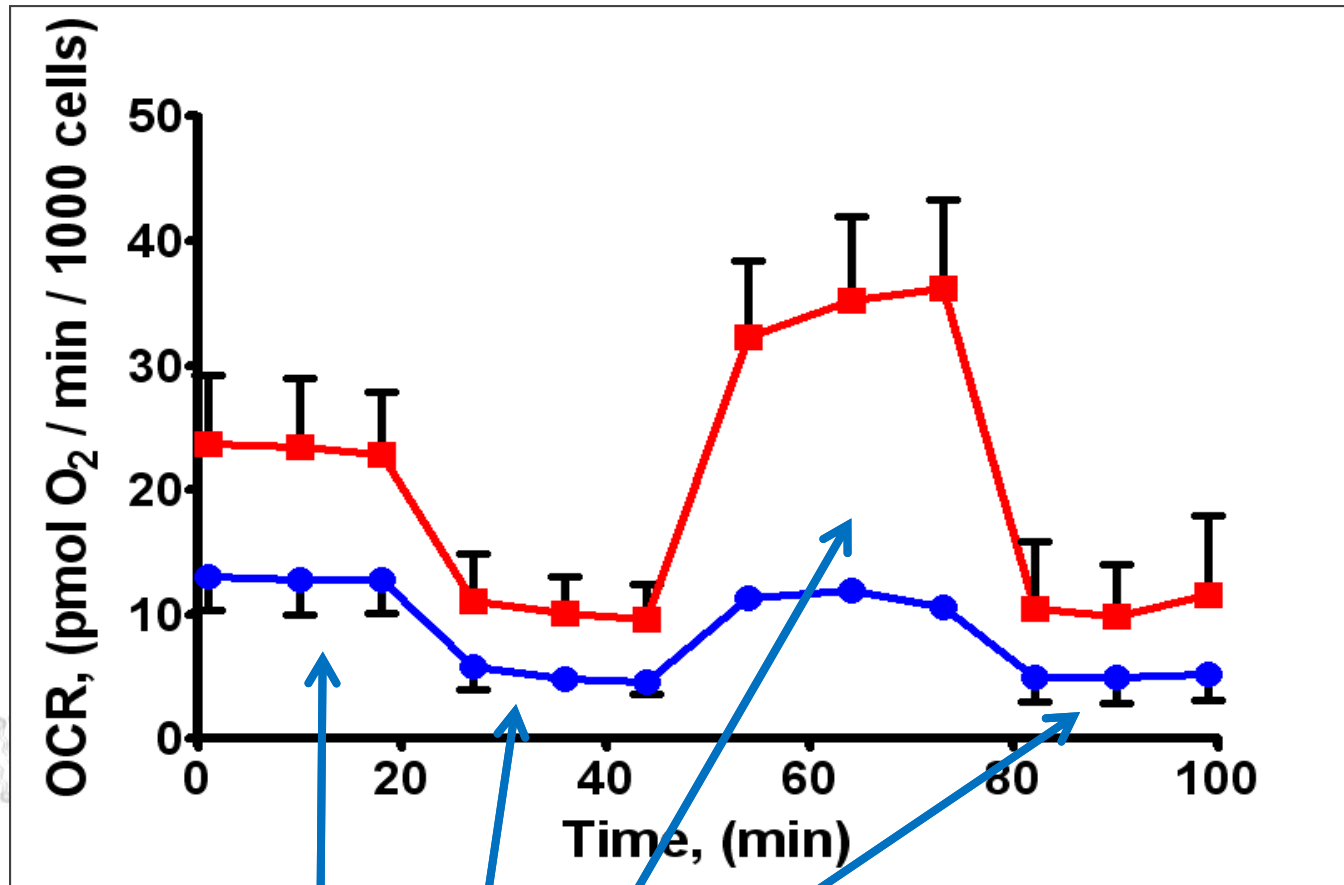
20 months



Mice deficient in CSB consumes more oxygen

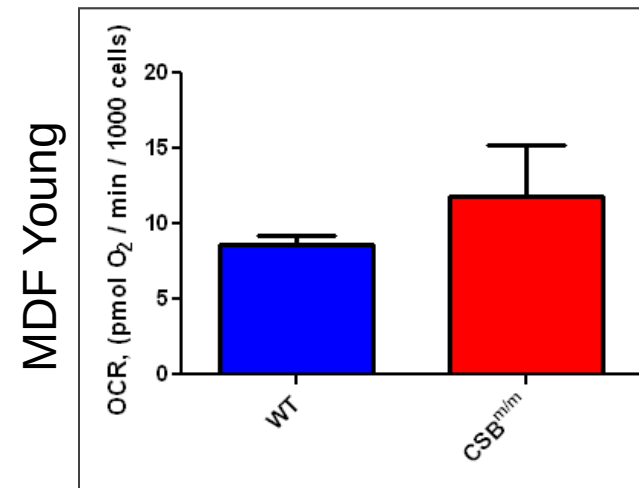
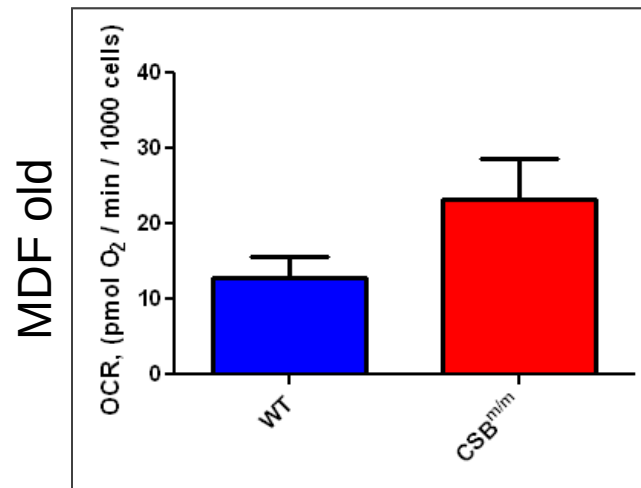
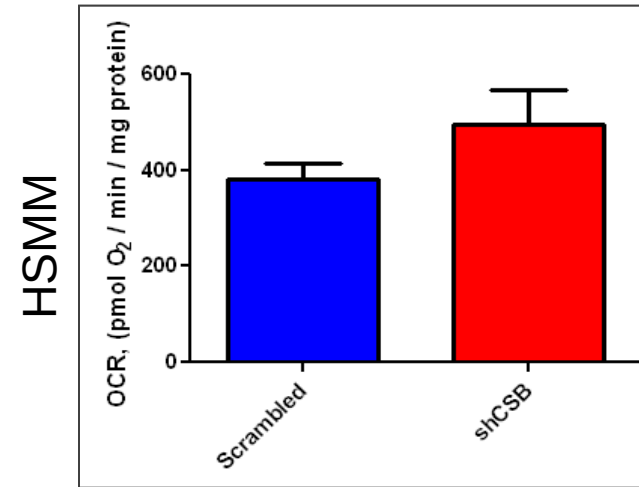
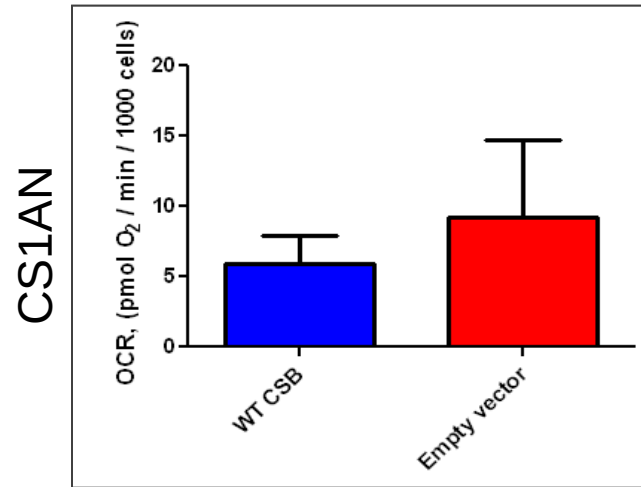


Sample Seahorse XF24 experiments



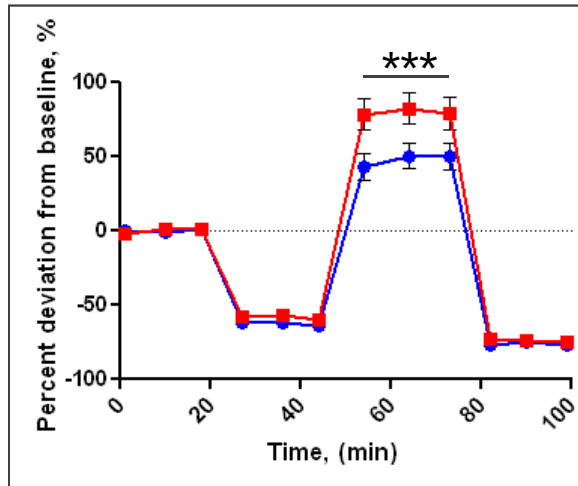
- Basal respiration rate
- Oligomycin is added to inhibit complex V
- FCCP uncouples respiration
- Antimycin A inhibits complex III

Basal oxygen consumption is increased in CSB deficient cells

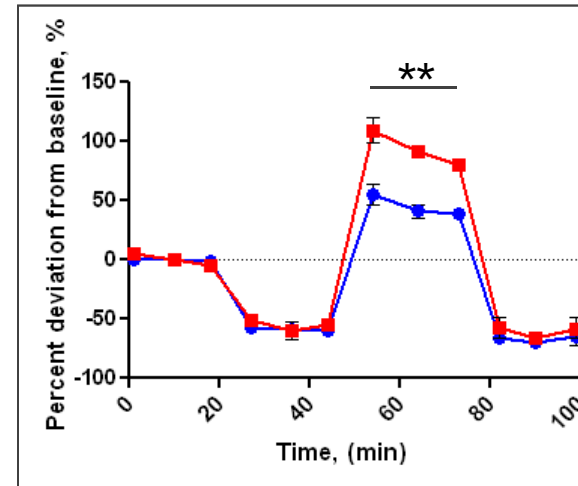


Spare respiratory capacity is increased in CSB deficient cells

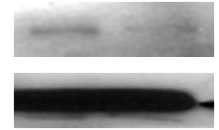
CS1AN



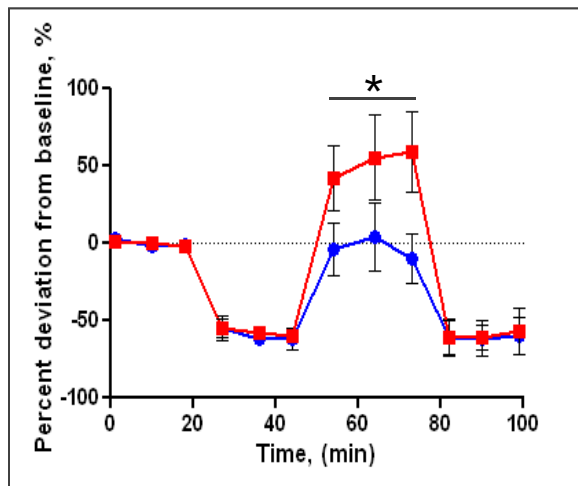
HSM



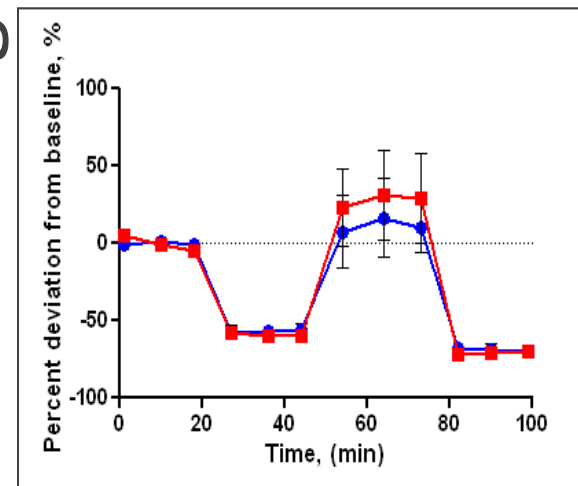
Ctrl
shCSB



MDF old

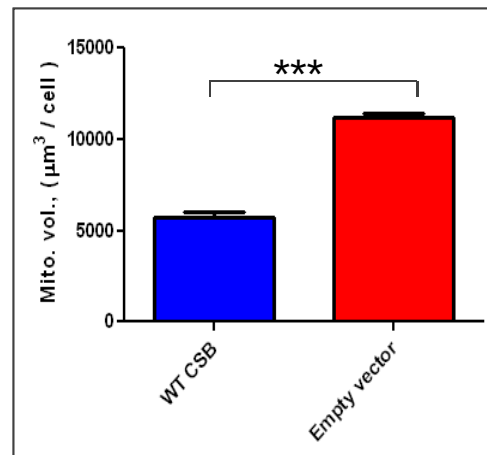
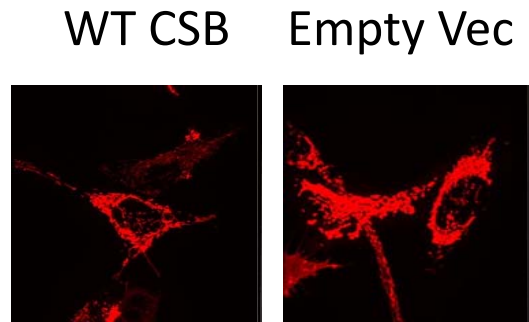


MDF Young

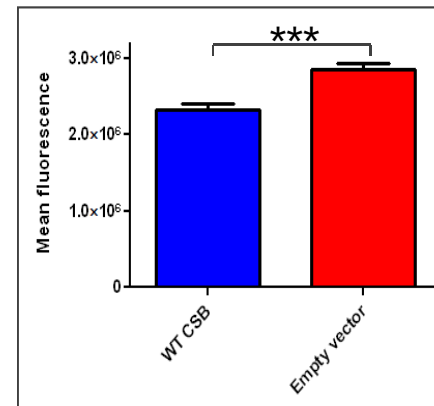
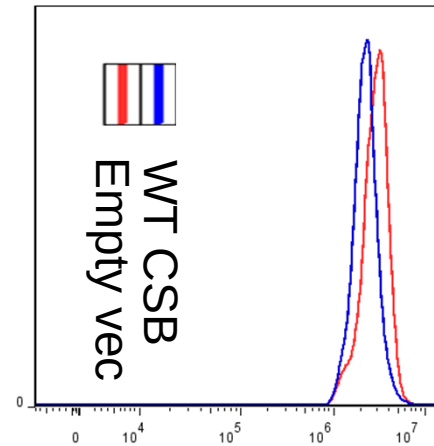


Control CSB deficient

Mitochondrial content is increased in CSB deficient CS1AN cells

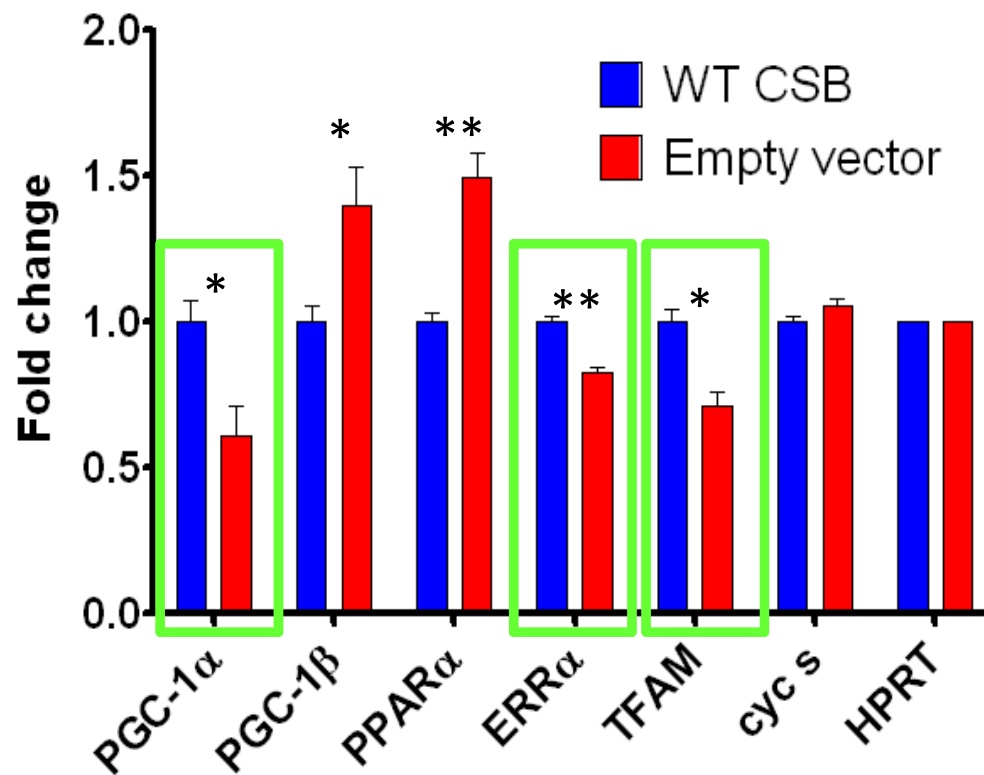


Mitochondrial
RFP-tagged protein



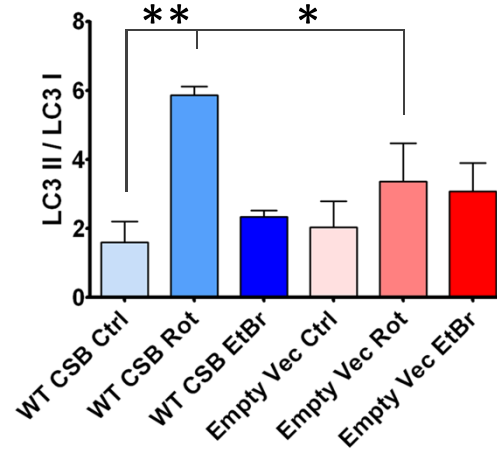
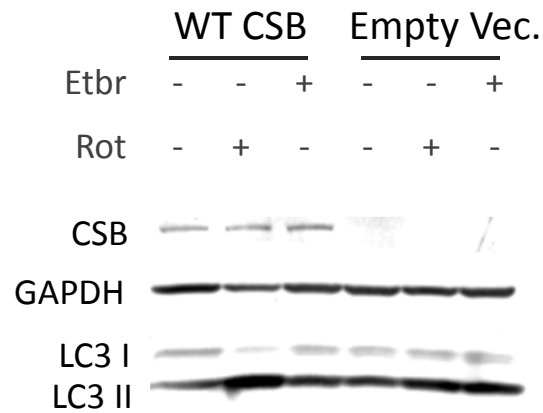
Mitotracker Green

Mitochondrial biogenesis cannot account for the increased mitochondrial volume in CSB deficient cells

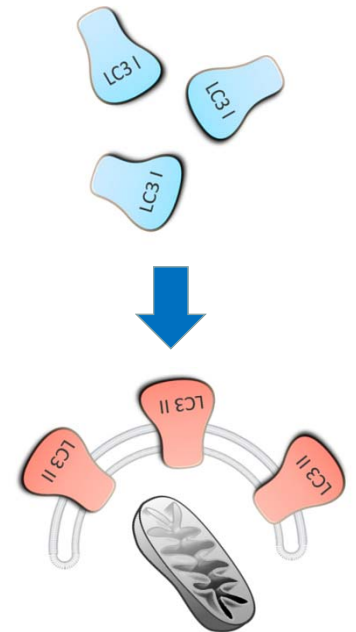
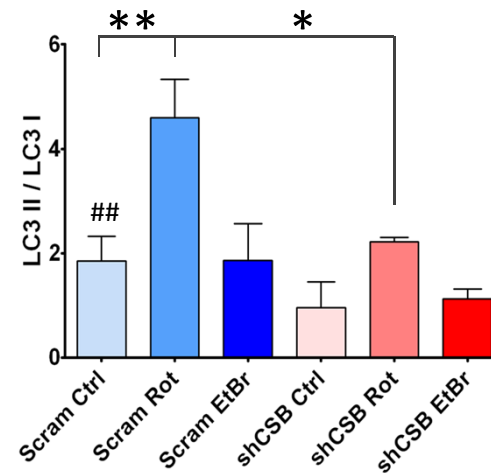
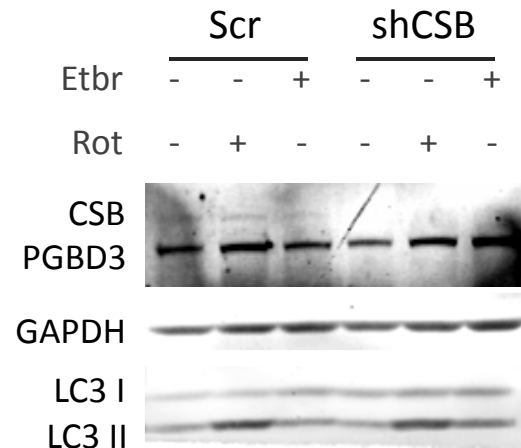


Autophagy is decreased in CSB deficient cells

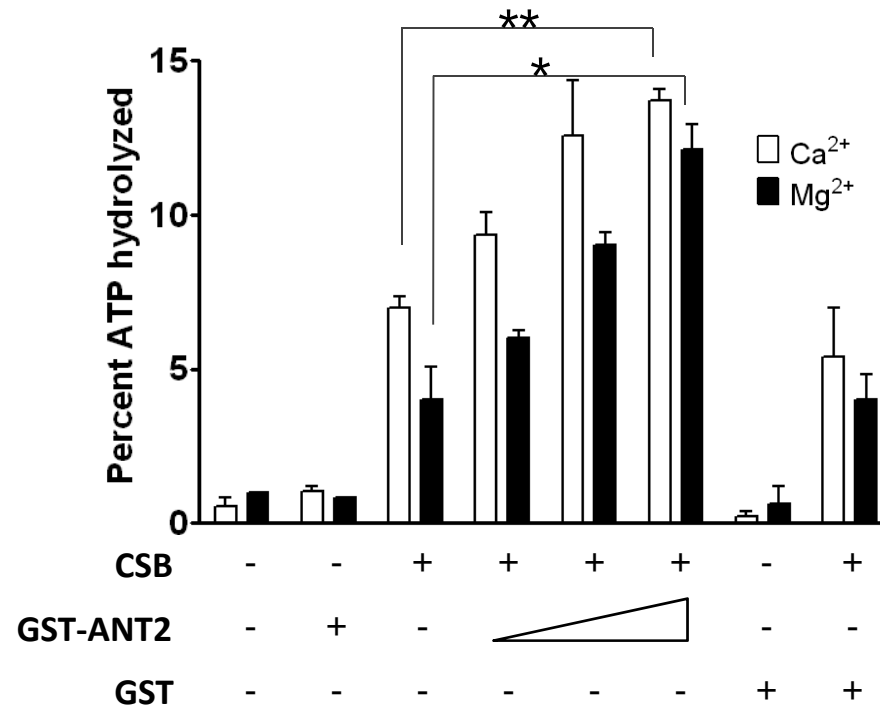
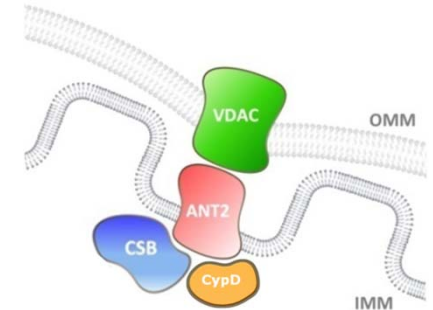
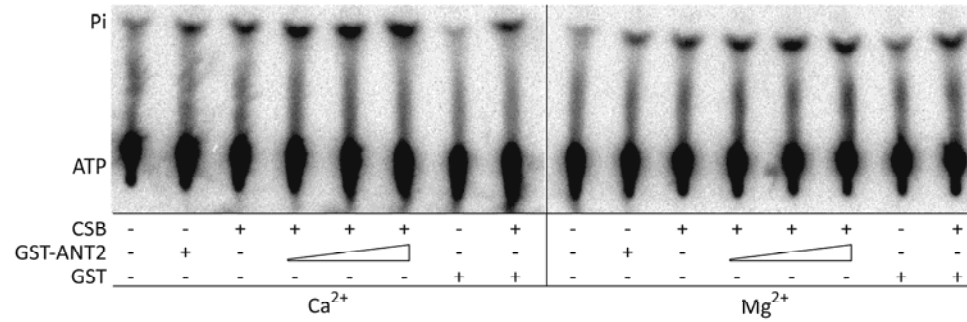
CS1AN



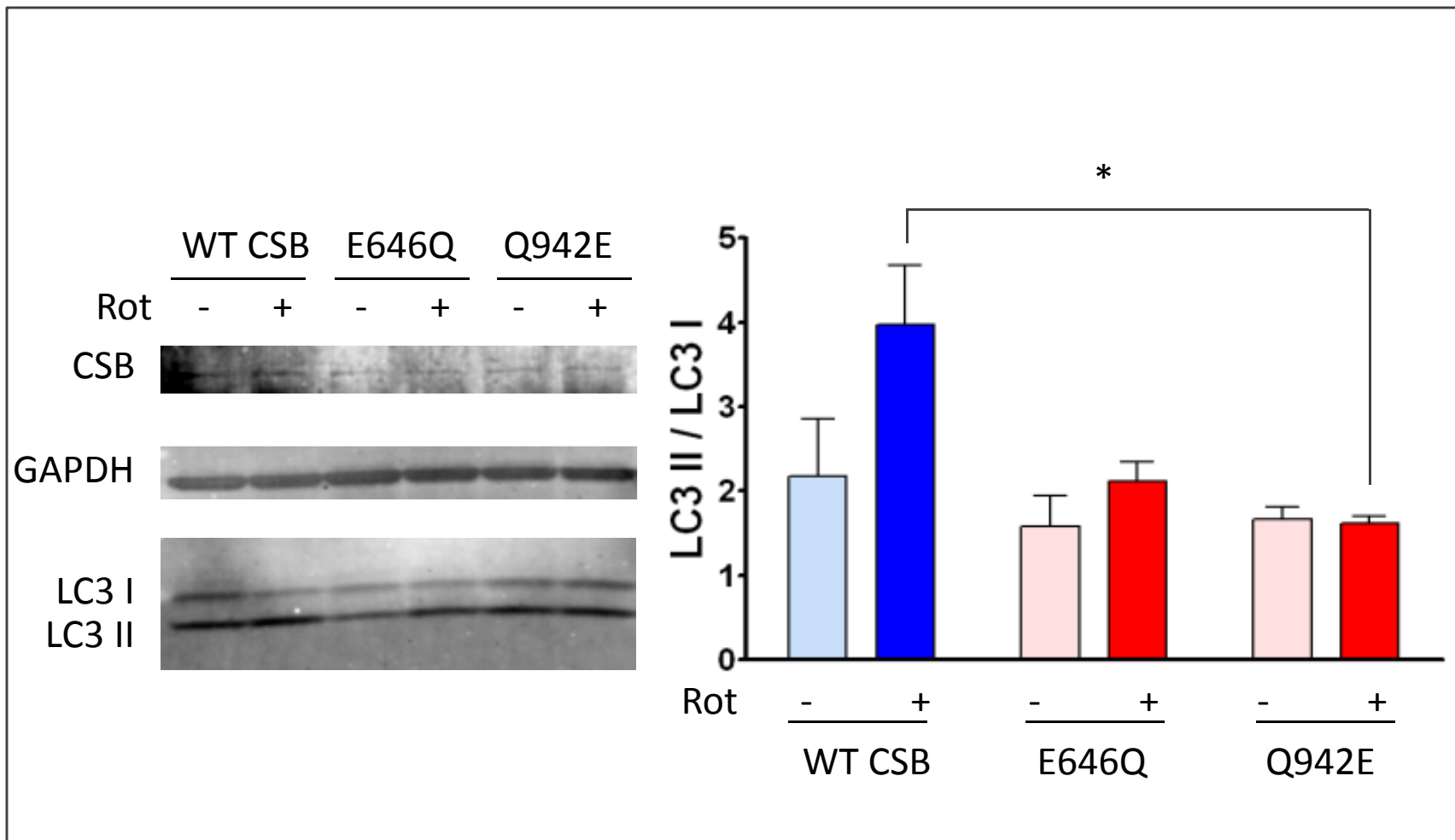
HSMM



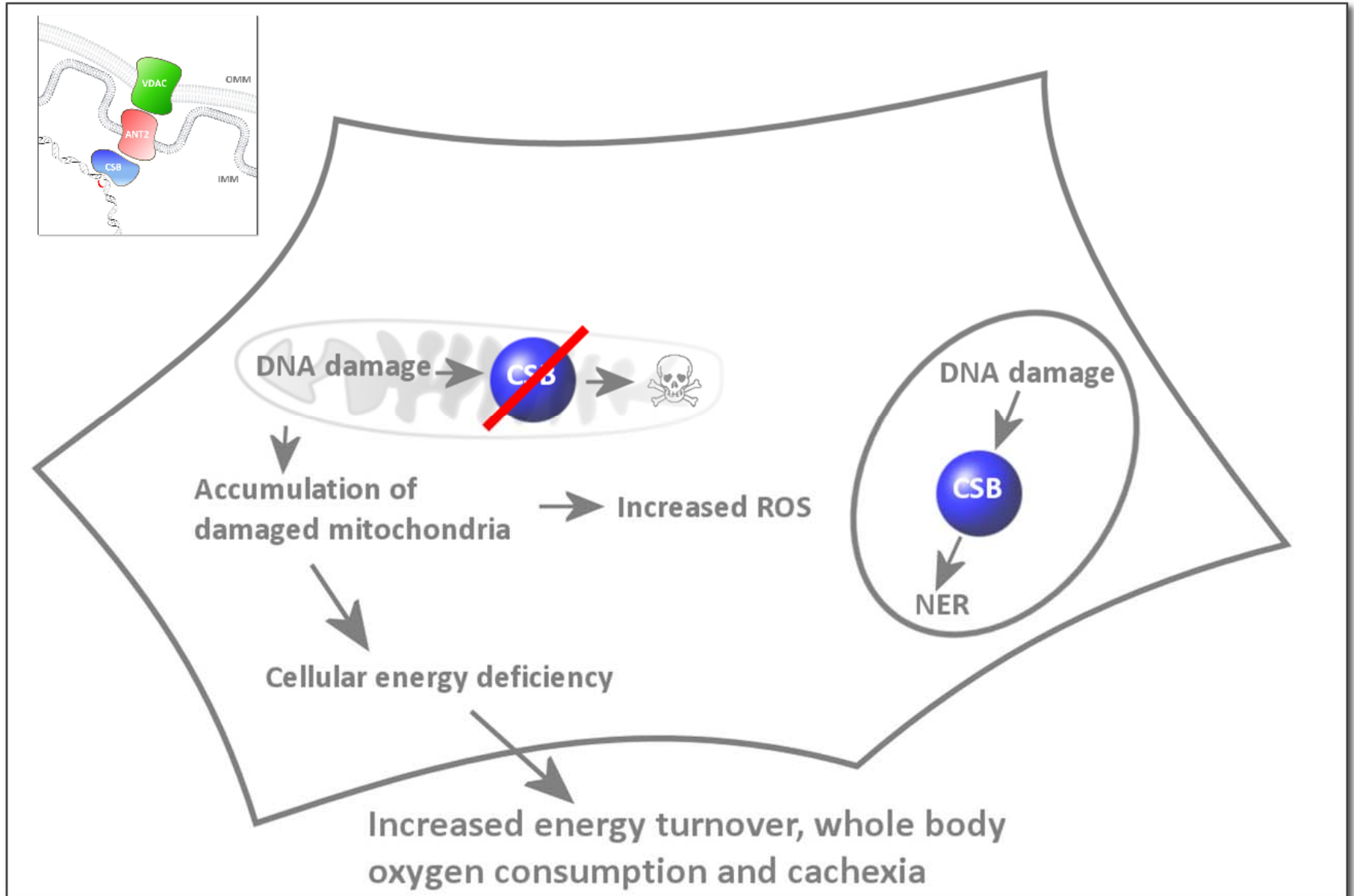
CSB functionally interacts with ANT2



Autophagy is dependent on the ATPase activity of CSB



Model



Acknowledgement

- Vilhelm A. Bohr
- Deborah Croteau
- Peter Sykora
- Scott Maynard
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Thank you for listening!

