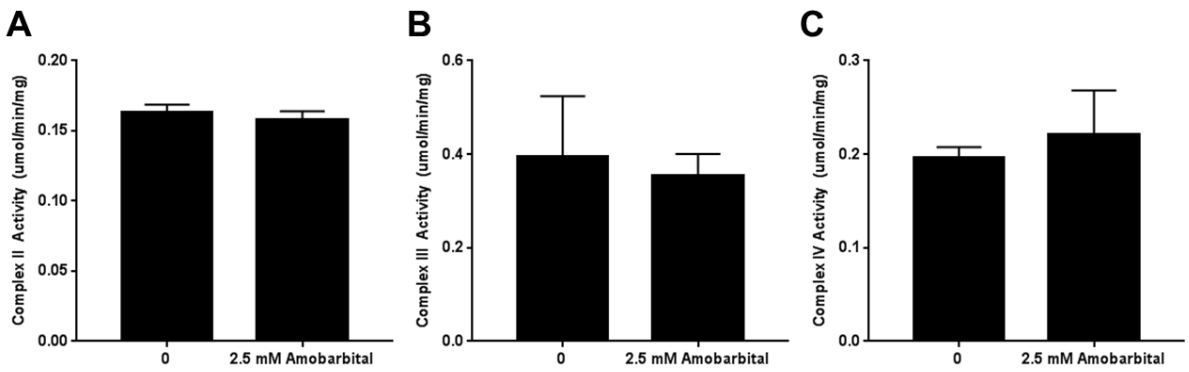

Fig. S1. Amobarbital does not inhibit complexes II, III, and IV of the ETC. (**A**) Complex II activity assayed spectrophotometrically as DCIP reduction by coenzyme Q in the presence and absence of succinate in primary bovine chondrocytes (n = 3, data represent the mean and standard deviation, no difference by student's t-test). (**B**) Complex III activity assayed spectrophotometrically as cytochrome c reduction by reduced coenzyme Q in primary bovine chondrocytes (n = 3, data represent the mean and standard deviation, no difference by student's t-test). (**C**) Complex IV activity assayed spectrophotometrically as the rate of oxidation of cytochrome c in primary bovine chondrocytes (n = 3, data represent the mean and standard deviation, no difference by student's t-test).

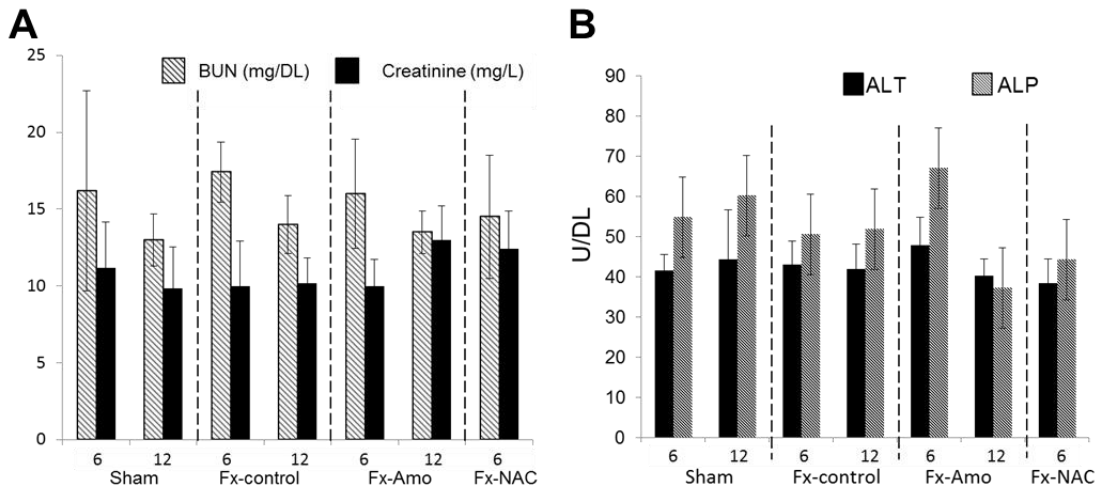

Fig. S2. Standard blood chemistry panel result 6 and 12 months after fracture. (**A**) Indicators of kidney health from standard blood chemistry panels run at harvest at 6 and 12 months after porcine IAF (n = 5 for sham, n = 5 for ORIF, n = 5 for ORIF + amobarbital, n = 6 for ORIF + NAC, data represent the mean and standard deviation with no differences noted via two way ANOVA). (**B**) Indicators of liver health from the same blood chemistry panels 6 and 12 months after porcine IAF (n = 5 for sham, n = 5 for ORIF, n = 5 for ORIF + amobarbital, n = 6 for ORIF + NAC, data represent the mean and standard deviation with no differences noted via two way ANOVA). Normal ranges for domestic pigs are BUN 9 – 30 mg/DL; Cre 1.2 – 2 mg/DL; ALT 20 – 48 U/L; ALP 49 – 83 U/L.

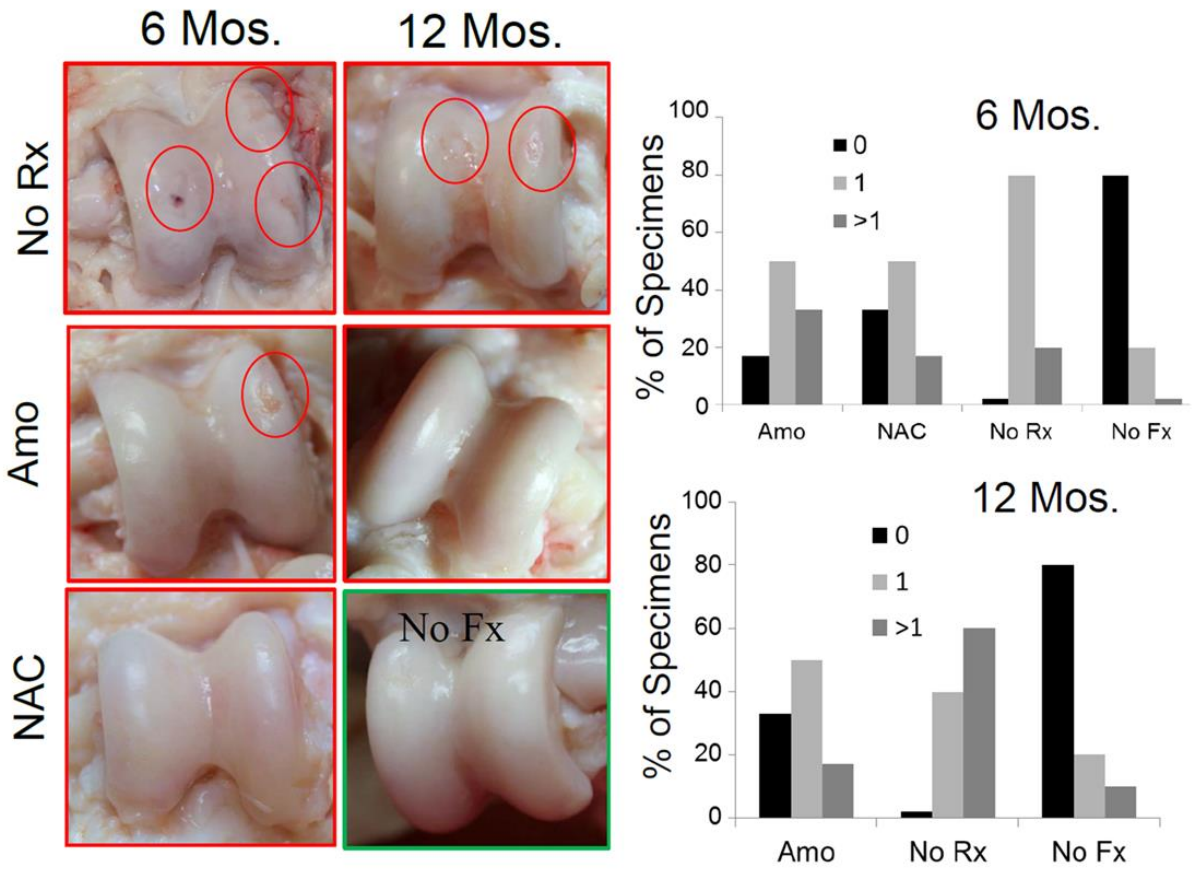

Fig. S3. PTOA is macroscopically apparent by 6 months without treatment. Representative macroscopic pictures of porcine talus specimens harvested 6 and 12 months post-IAF. Images are focused where lesions are concentrated and most severe, and represent higher lesion counts on no treatment (No Rx) ORIF tali that show a trend towards an increase over all other groups at 6 months ($P = 0.16$ by chi-squared test) that reaches significance by 12 months relative to all other groups ($P = 0.04$ by chi-squared test). Histograms show the percentage of tali possessing 0, 1, and greater than 1 lesion.

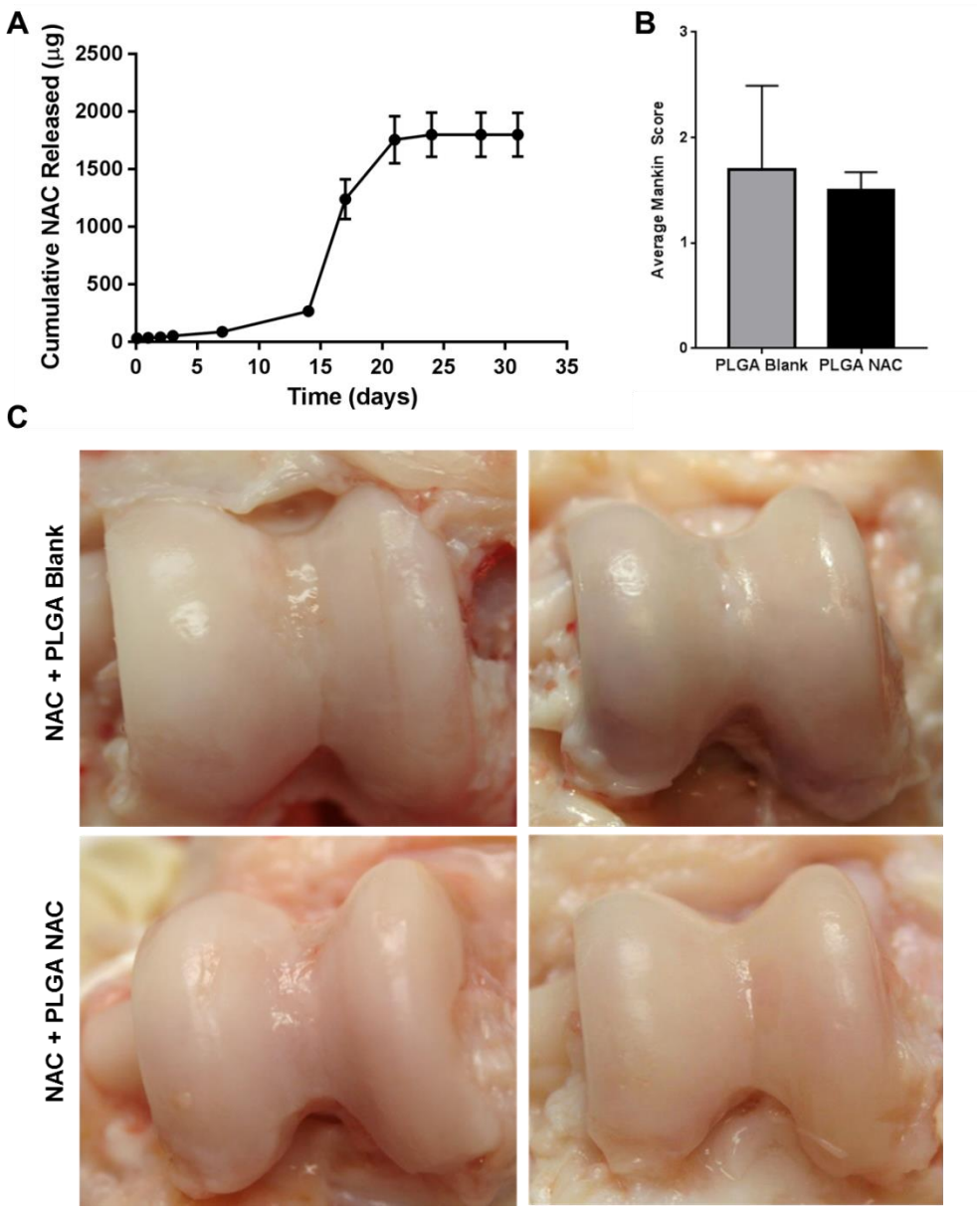

Fig. S4. Sustained release of NAC does not augment NAC efficacy at 6 months. (**A**) Cumulative release of NAC from the PLGA pellet into solution assayed spectrophotometrically using Ellman's reagent (n = 3, circles represent the mean and standard deviation is shown, significant release occurs ~17 days after implantation, $P < 0.01$ via one way ANOVA). (**B**) Semiquantitative Mankin scoring of the porcine talar surfaces treated with only acute NAC (PLGA Blank) or acute NAC and extended release NAC (PLGA NAC) then harvested 6 months

post-IAF (n = 3 for both groups, mean and standard deviation are shown, no significant differences by two way ANOVA with Dunnett's post-test). (**C**) Representative, macroscopic harvest images from either PLGA Blank or PLGA NAC treated animals (n = 3).

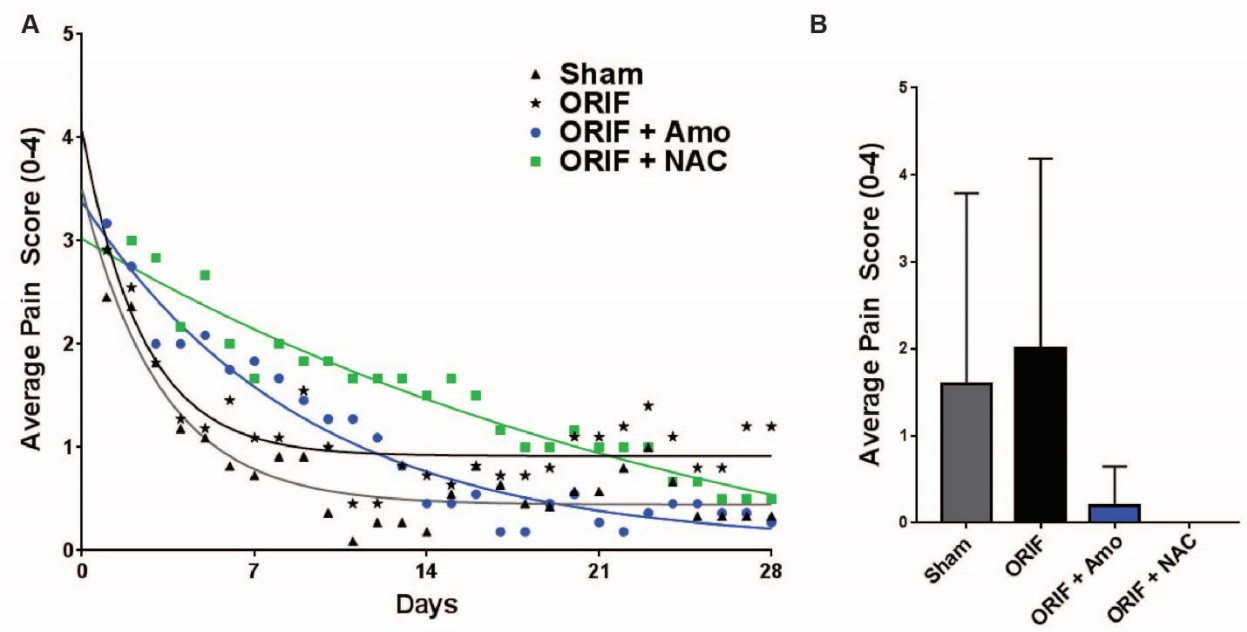

Fig. S5. Amobarbital and NAC improve pain scores at 6 months but not during recovery. (**A**) Average pain score over the first four weeks after porcine IAF (n = 11 for sham, n = 11 for ORIF, n = 12 for ORIF + amobarbital, n = 6 for ORIF + NAC, points represent the mean and lines represent a regression of the entire group). (**B**) Average pain score in the 2-3 days prior to euthanasia 6 months post-IAF (n = 5 for sham, n = 5 for amobarbital, n = 6 for NAC, data represent the mean with standard deviation shown).

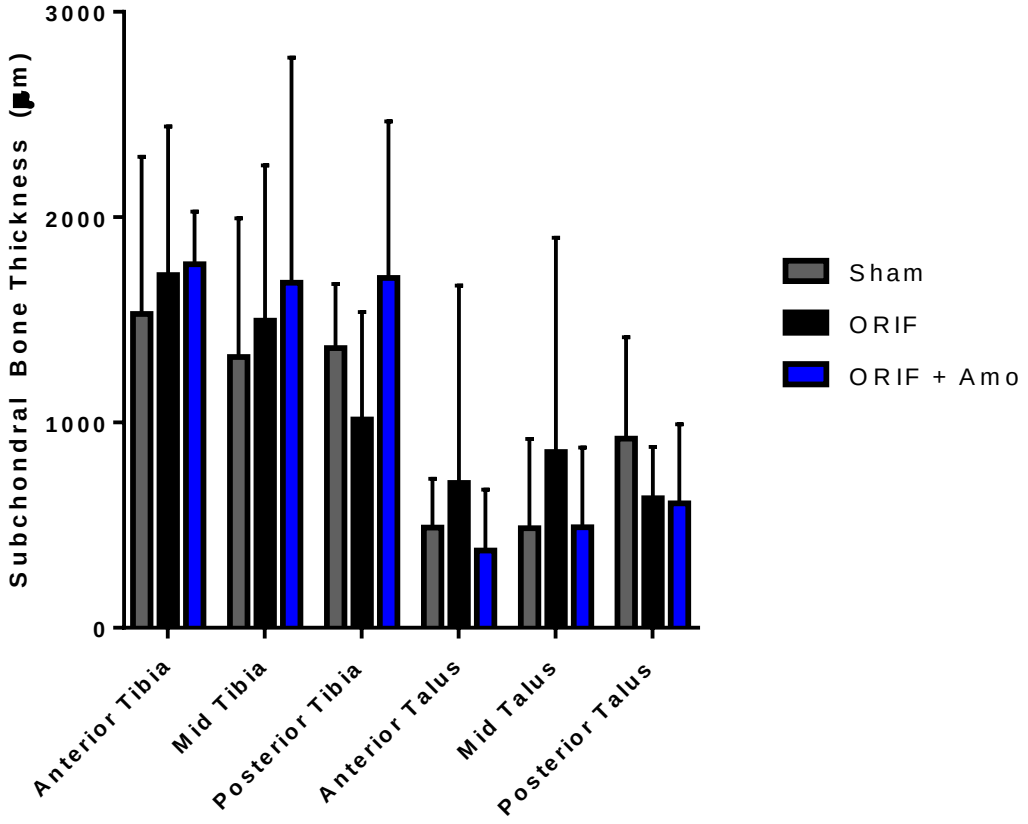

Fig. S6. Histology shows highly variable subchondral bone thickness 12 months after IAF. Thickness profiles for sham, ORIF, and amobarbital treated porcine groups thoughout the joint (n = 6 for sham and ORIF, n = 7 for ORIF + Amo, data represent the mean and standard deviation, no difference noted via two way ANOVA with Dunnett's post-test).

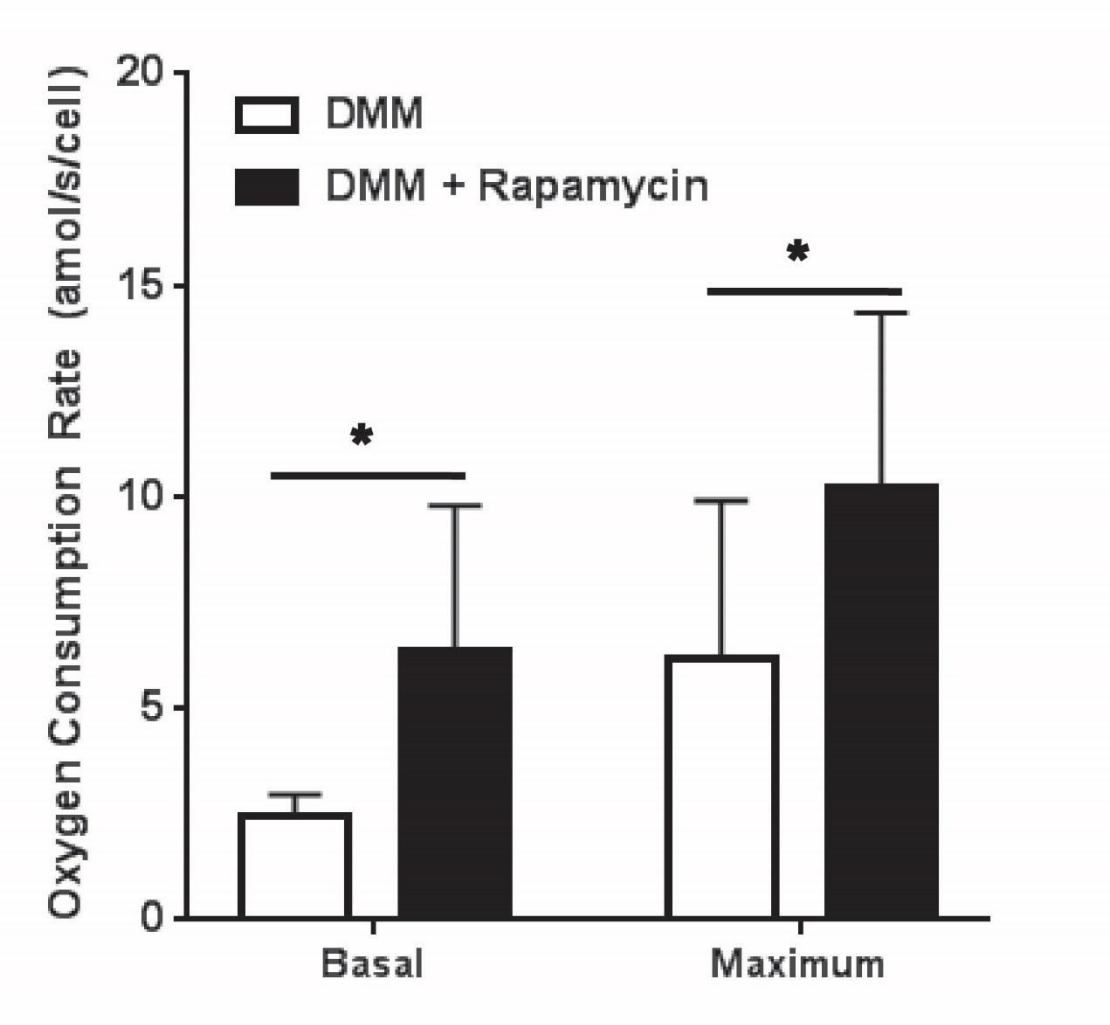

Fig. S7. Intra-articular rapamycin reverses mitochondrial dysfunction after meniscal injury. At 4 weeks after destabilization of the medial meniscus (DMM), rabbit articular chondrocytes were harvested and analyzed via mitochondrial stress test (n = 6, * P-value < 0.01 DMM vs DMM + rapamycin via one way ANOVA).

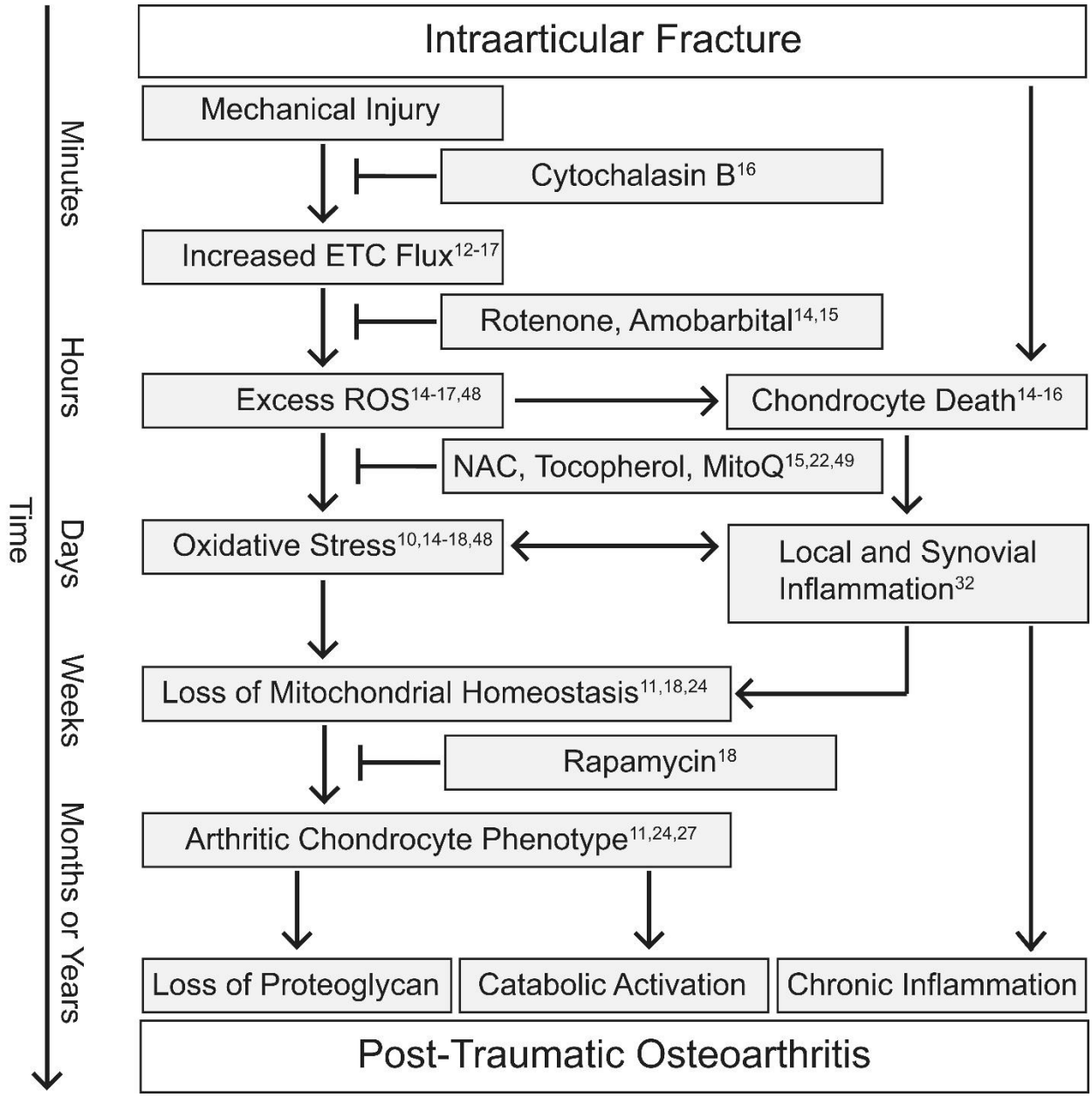

Fig. S8. Contributions of mitochondrial responses following IAF to PTOA. Contributions cited from prior work have been annotated on the figure to provide depth and scale for how each feature of the pathology contributing to PTOA might interact with the others over the course of chronic disease development.