Stem cell niche biomechanics in intestinal health and disease

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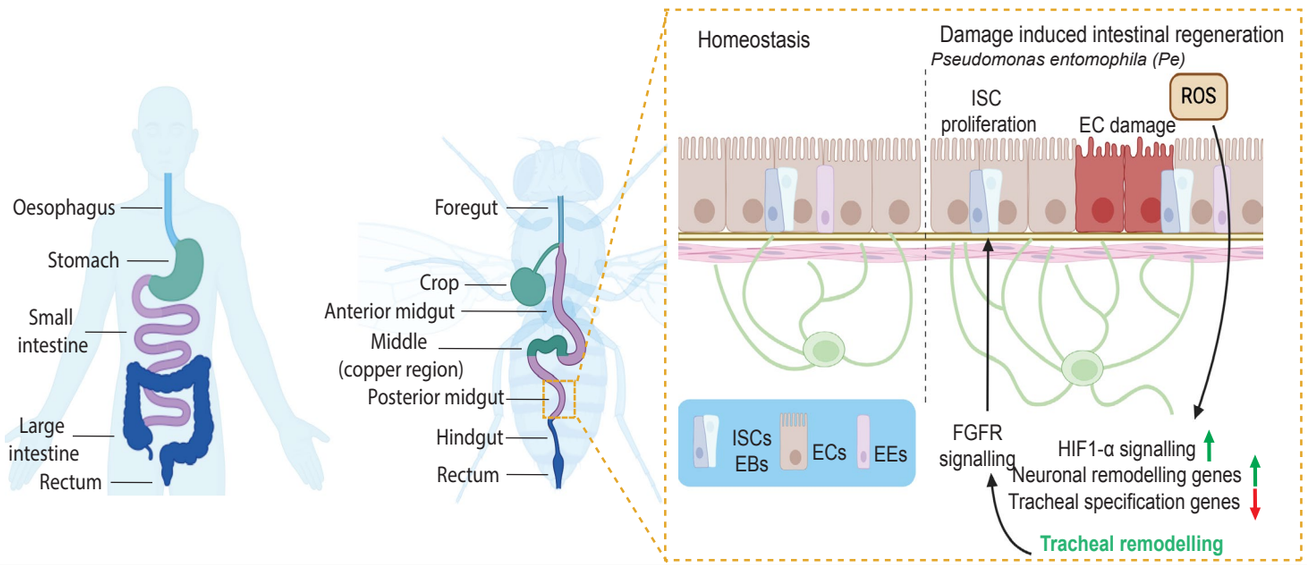
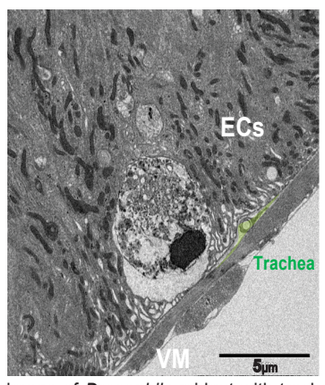
Background

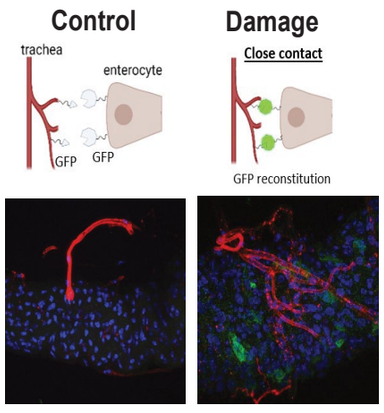
The adult *Drosophila* midgut, a functionally and anatomically analogous organ to the mammalian intestine, has provided invaluable insight into regulatory mechanisms that govern intestinal stem cell (ISC) behaviour. Upon damage, the midgut undergoes cellular and tissue-wide morphological changes. Compensatory ISC proliferation maintains tissue integrity following damage, whereby reciprocal crosstalk between the midgut epithelium and the vascular-like tracheal system is essential for ISC proliferation (Perochon et al. 2021; Tamamouna et al. 2021). While biochemical trachea-gut crosstalk is appreciated, the biomechanical consequences of intestinal damage and implications for the trachea remain less so. Data from the Cordero lab demonstrates an evolutionary conserved role for the mechanosensitive ion channel Piezo in the gut vasculature for regeneration following damage induced mechanical changes within the intestinal epithelium.



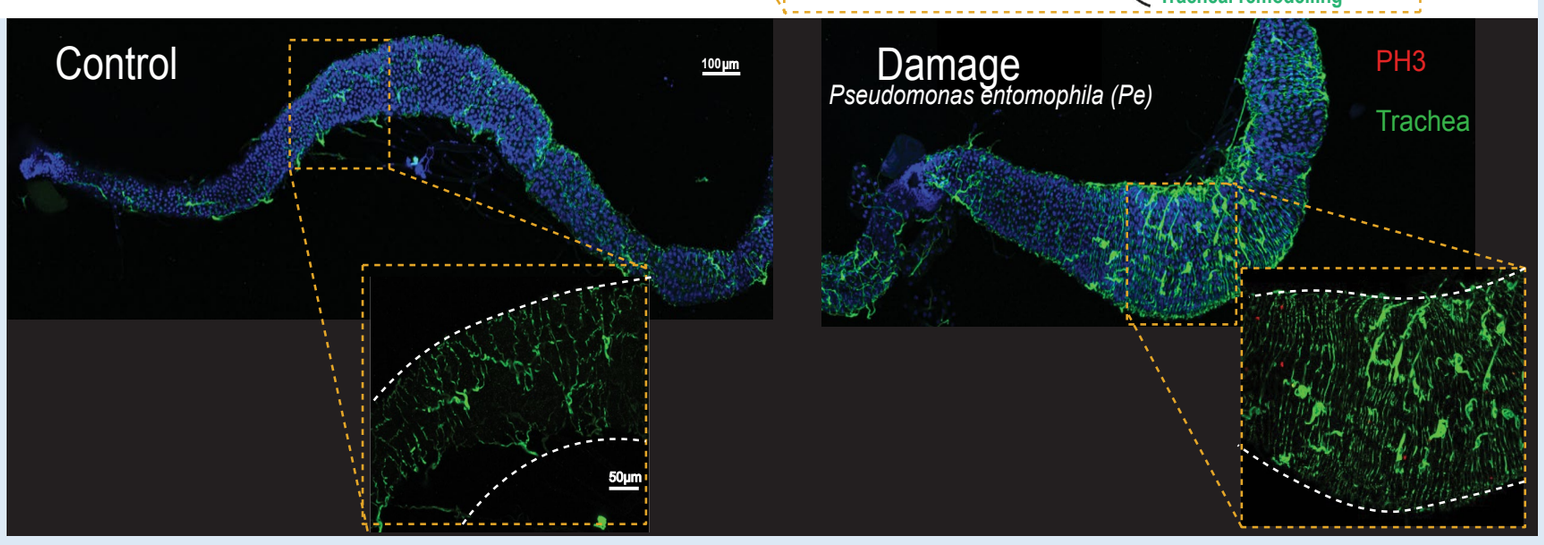
1. Intestinal trachea directly contacting enterocytes



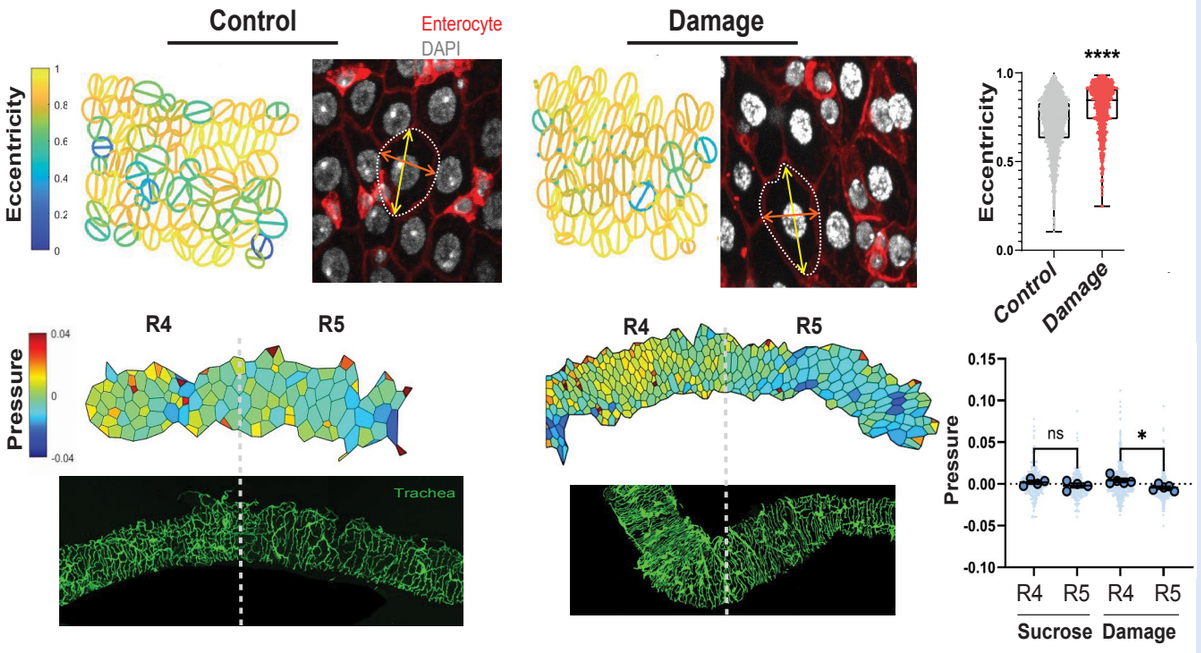
TEM image of *Drosophila* midgut with trachea (green), enterocytes (ECs) and visceral muscle (VM).



Reconstitution into functional GFP molecule upon damage

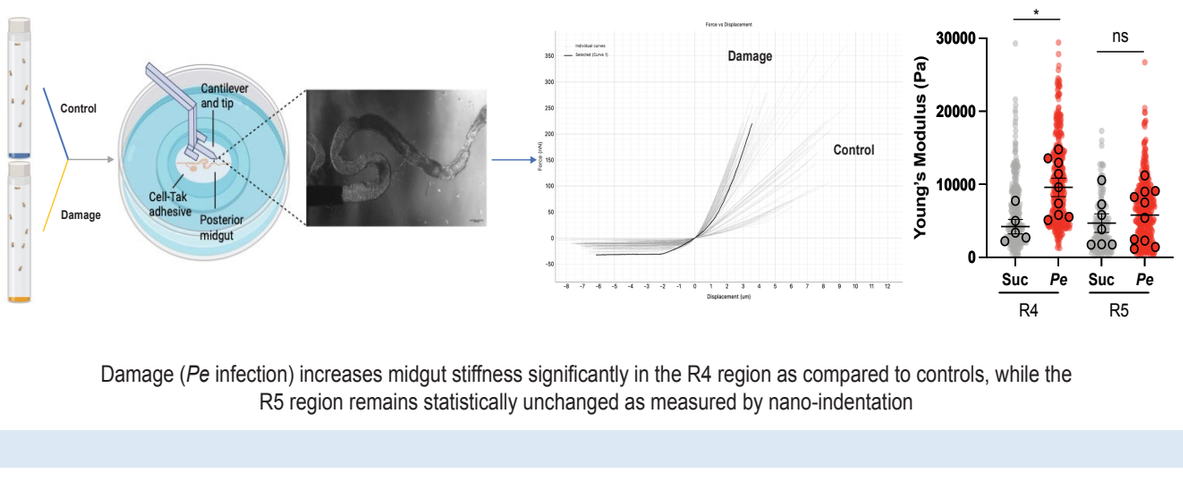


2. Damage alters enterocyte morphology and epithelial pressure



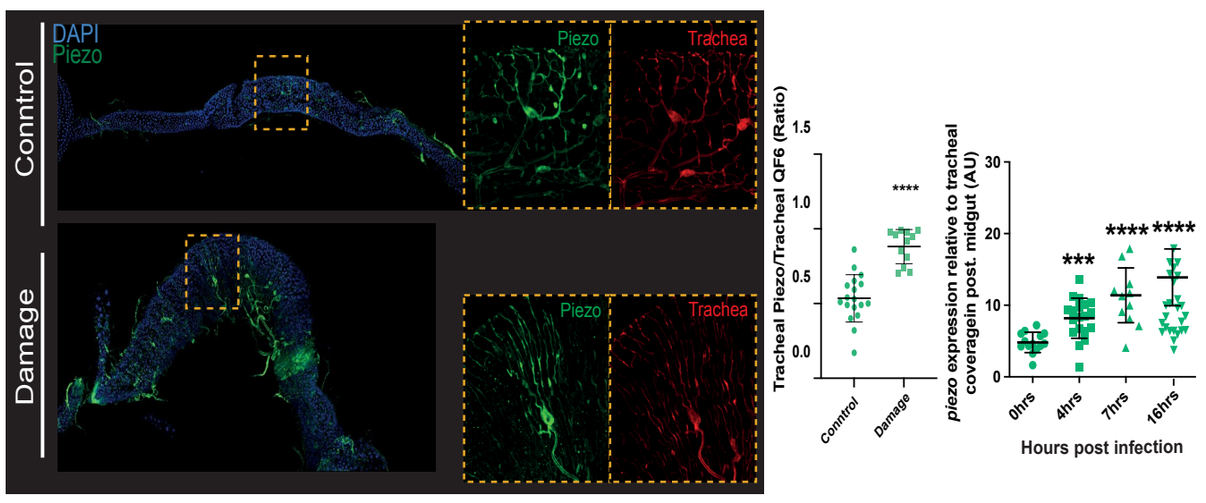
Enterocyte eccentricity increases in the posterior midgut upon damage. Analysing enterocyte cell morphology using Bayesian Force Inference shows an increase in pressure in the R4 midgut region, in line with increased tracheal remodelling in this area.

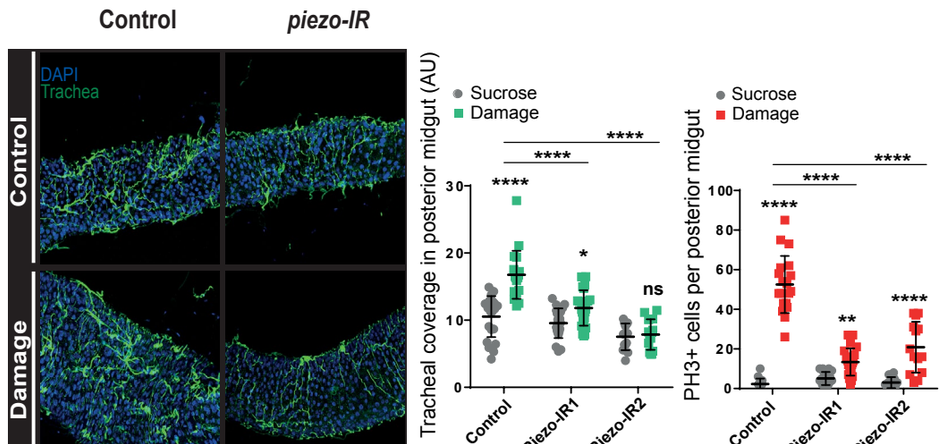
3. Mechanical characterisation of the midgut upon damage



Damage (*Pe* infection) increases midgut stiffness significantly in the R4 region as compared to controls, while the R5 region remains statistically unchanged as measured by nano-indentation

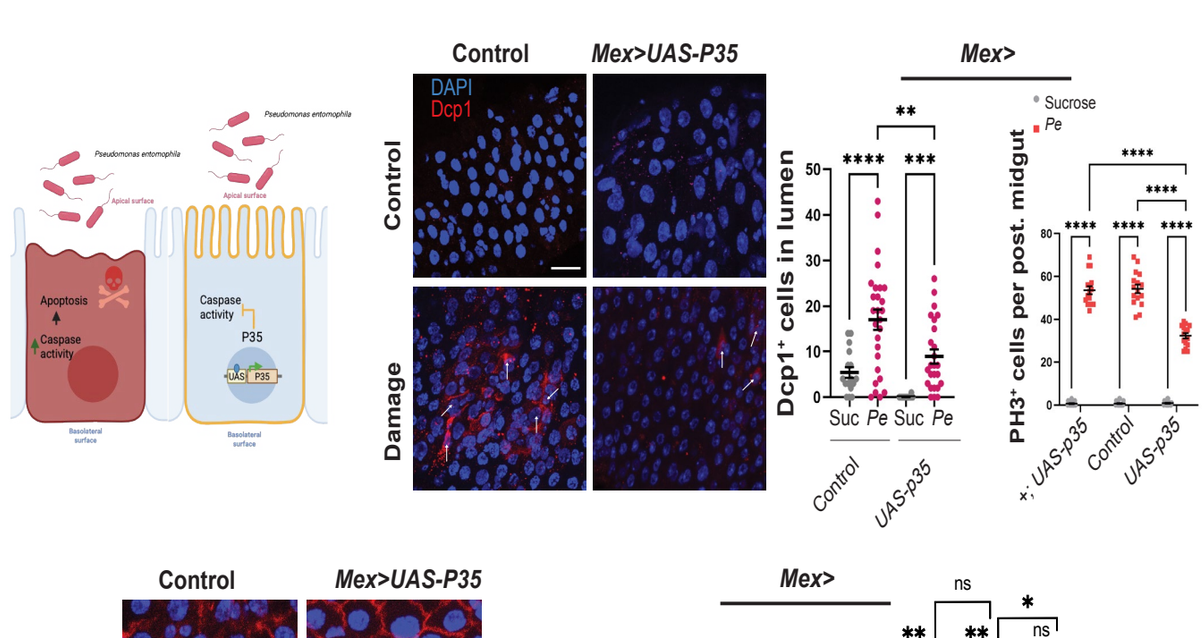
4. *piezo* upregulation upon damage drives tracheal remodelling

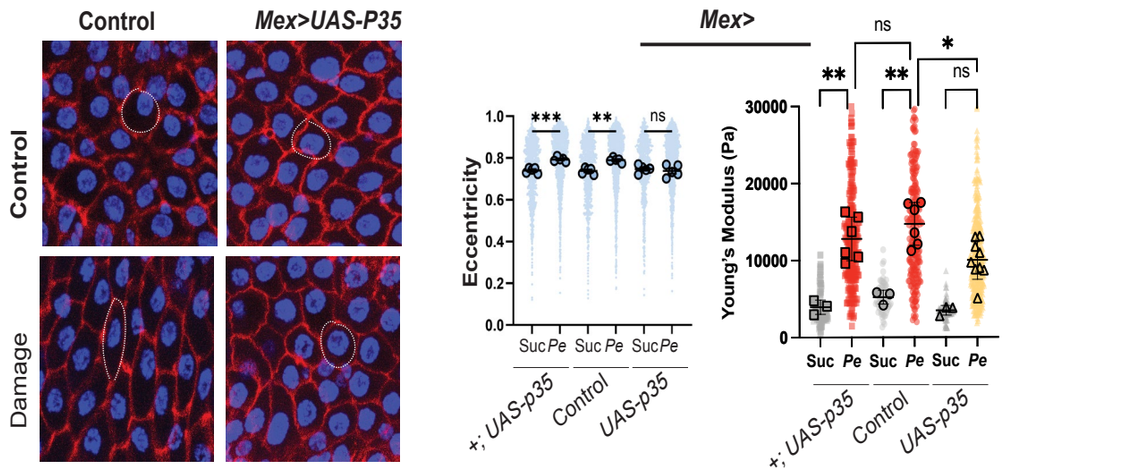




piezo expression increases independently of increase in overall tracheal coverage following damage and increases throughout an infection timecourse. Piezo is required for regenerative tracheal remodelling and ISC proliferation following damage to the midgut

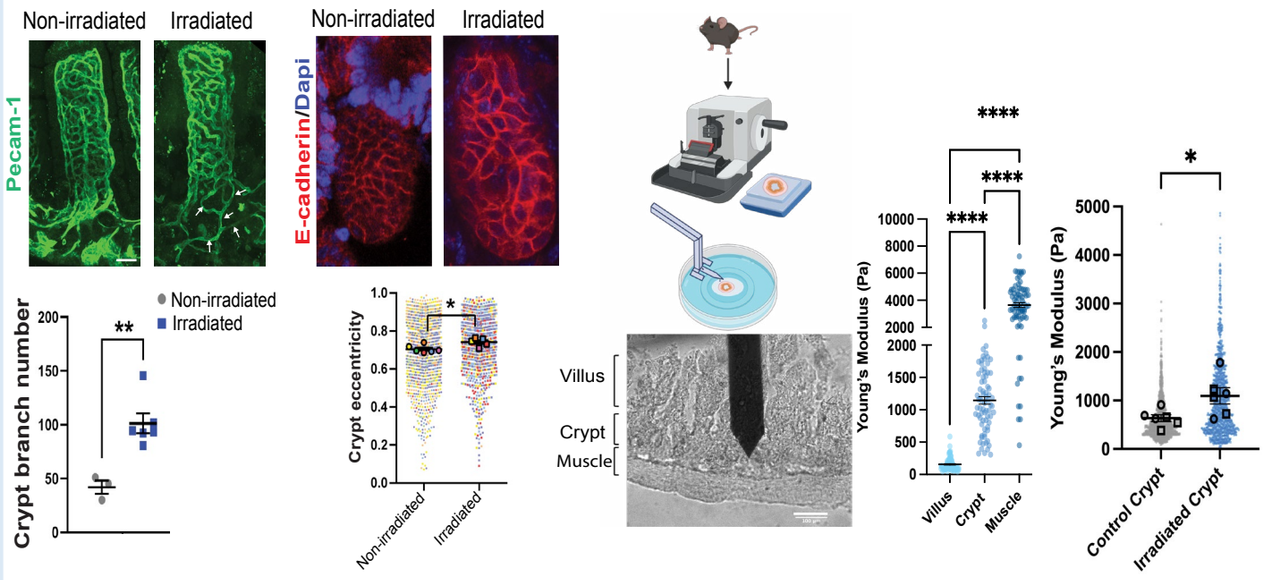
5. Epithelial cell death drives mechanical changes in the midgut





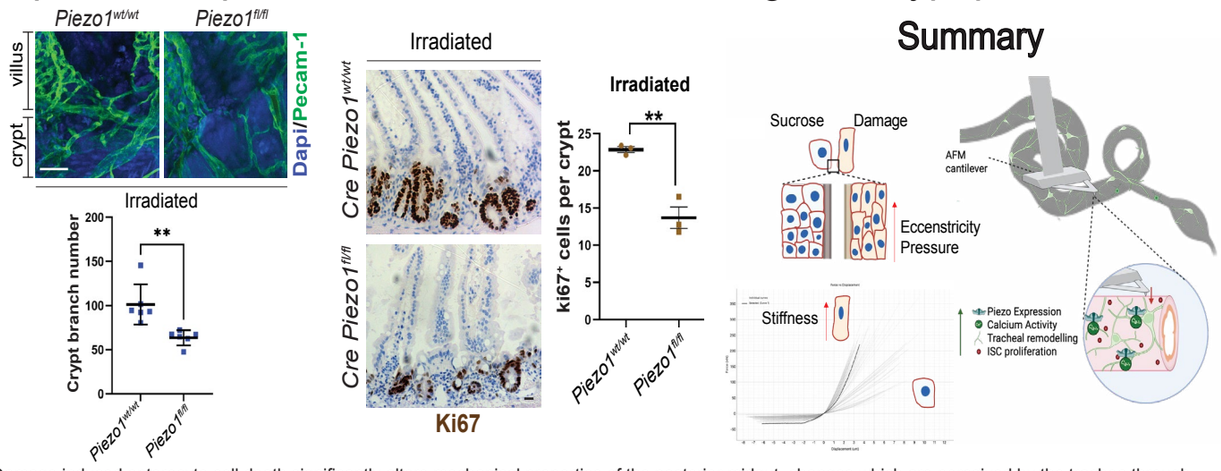
Midgut damage increases cell death and ISC proliferation, both can be reduced by driving *P35* expression in enterocytes. Additionally, eccentricity and stiffness can be reduced significantly by inducing P35 expression in enterocytes as compared to controls.

6. Whole body irradiative damage results in crypt stiffening and vascular remodelling in mouse small intestine



Whole body irradition results in increased crypt vascular branching and crypt cell eccentricity. Small intestine sections (30µm) maintain expected mechanical profile across transversal axis following cryosectioning. Crypt mechanics are significantly changed upon whole body irradiation.

7. *piezo 1* expression for vascular branching and crypt proliferation



Damage induced enterocyte cell death significantly alters mechanical properties of the posterior midgut, changes which are perceived by the trachea through mechanosensitive ion channel Piezo. Piezo activity and expression is required for both tracheal remodelling and regenerative ISC proliferation. In the murine small intestine endothelial *Piezo1* knockout results in decreased vascular branching and fewer proliferating crypts upon exposure to whole body irradiation.

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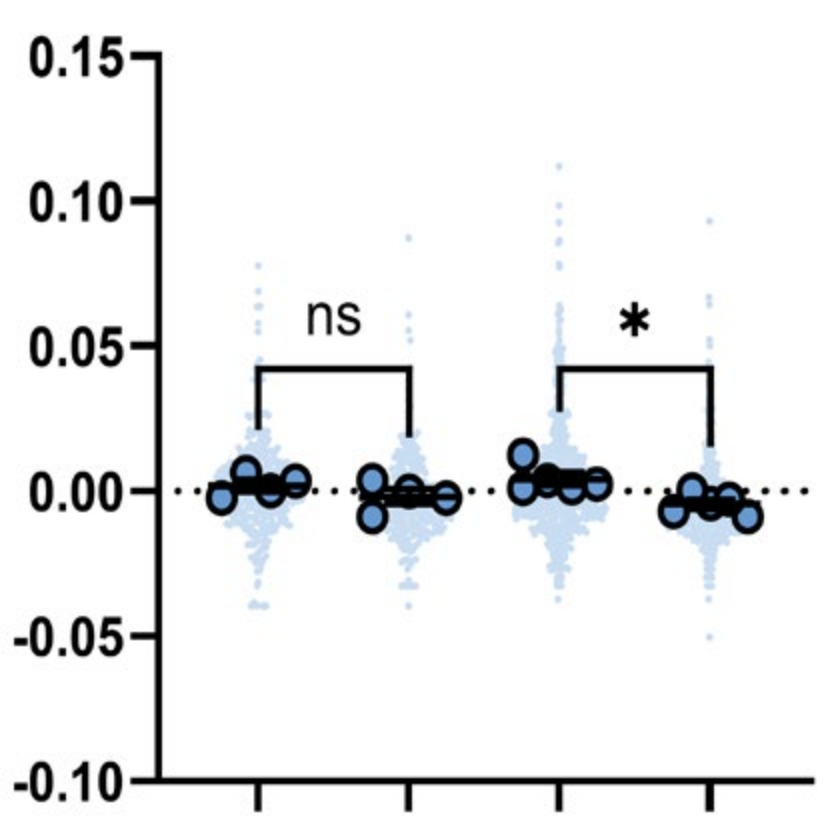
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