Intestinal injury precedes dysbiosis in a mouse model for pelvic irradiation

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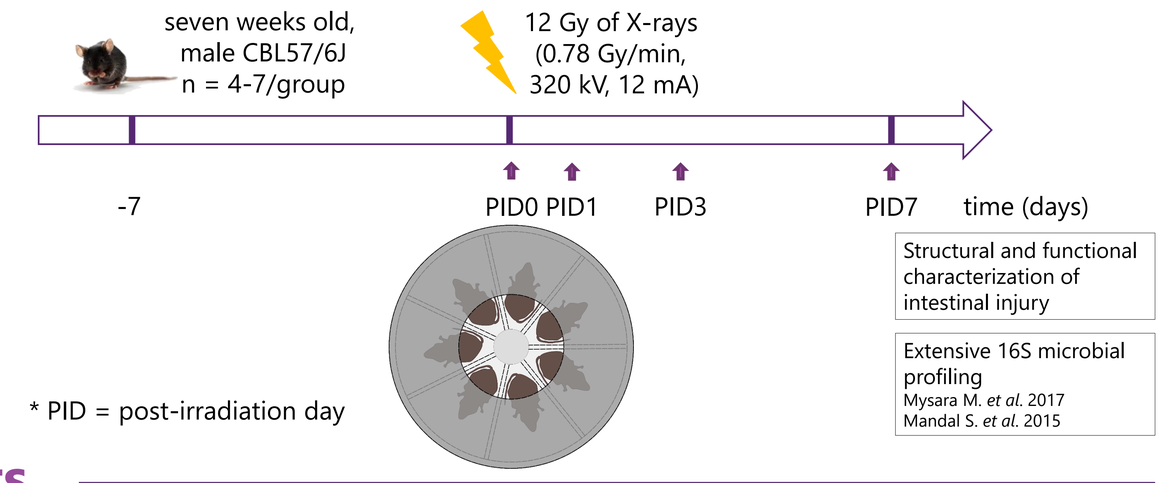
Introduction

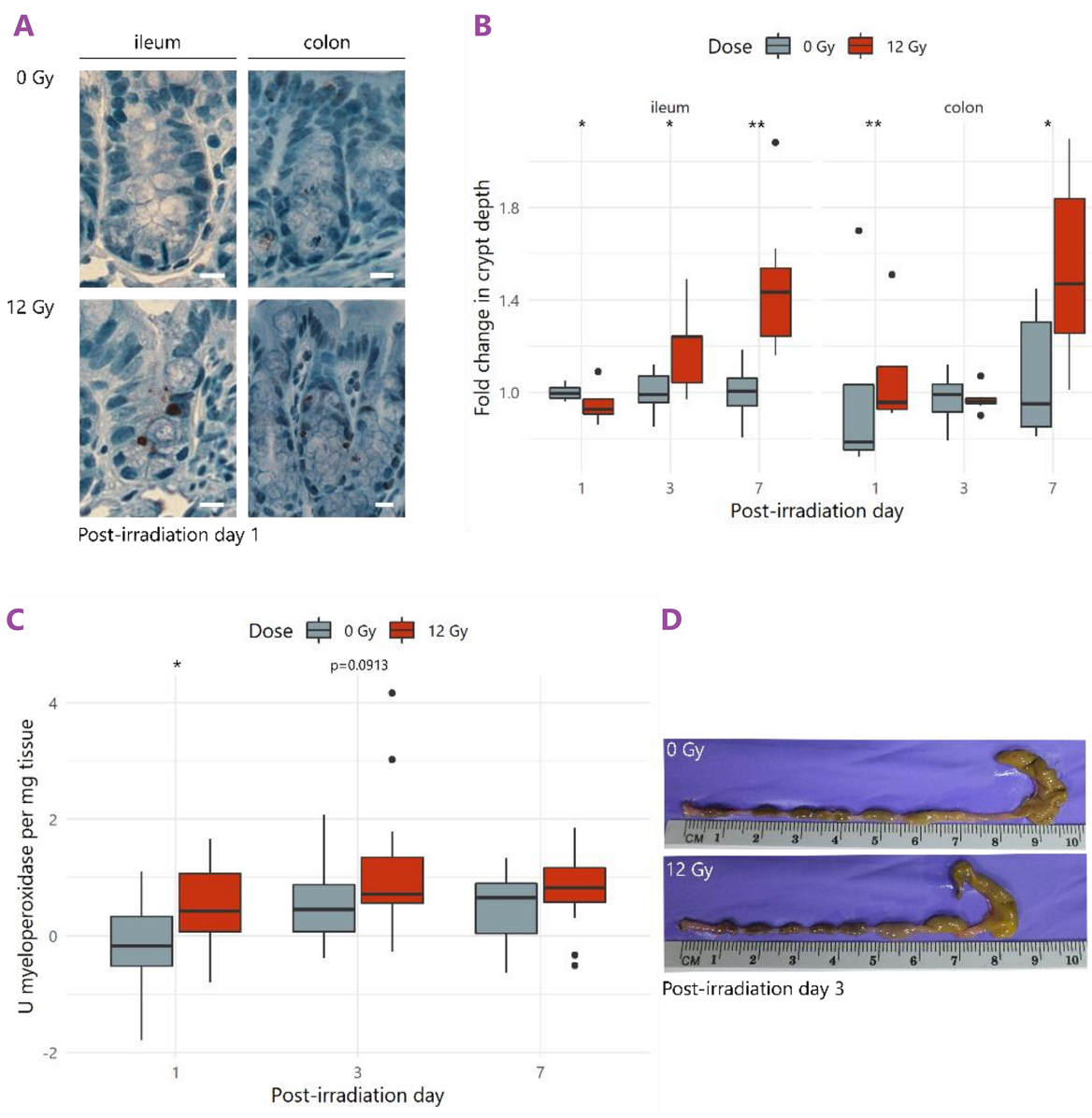
Pelvic radiotherapy is known to evoke **intestinal injury** and **dysbiosis**. Currently, there are no effective therapies available to mitigate these, which is in part due to the fact that the events causing intestinal injury and dysbiosis are not well understood. Additionally, whether a dysbiotic microbial community represents the **cause or consequence** of the disease state is still unknown.

In this study, the complex interplay between the murine host and its microbiome following acute pelvic irradiation was mapped by characterizing induced mucositis along with extensive 16S microbial profiling.

Methods

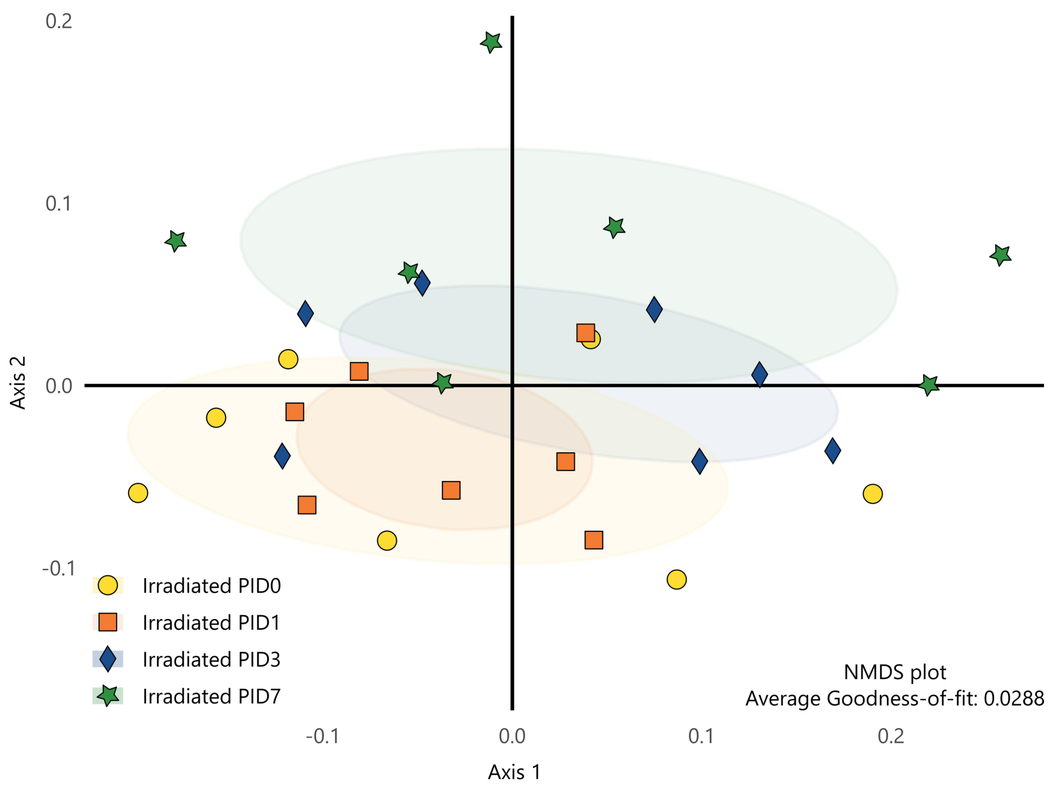


Results

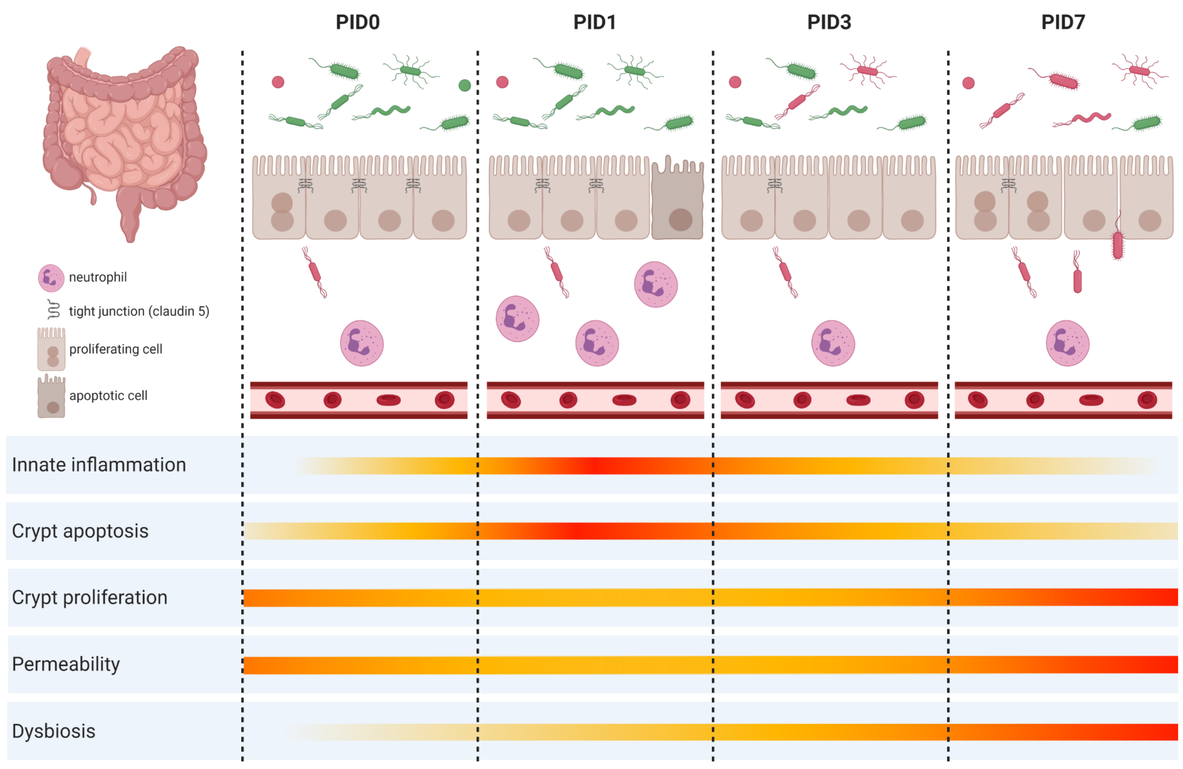


▲ **Figure 1. Pelvic irradiation acutely evokes intestinal injury**
A-B. Pelvic irradiation induced morphological changes in the intestine, as illustrated by (A) increased crypt apoptosis (TUNEL⁺ cells in brown) at PID1 and (B) changes in crypt depth, n=4-7 per group. **C-D.** Pelvic irradiation evoked a rapid inflammatory response, as measured by (C) myeloperoxidase activity, indicative of mucosal neutrophil infiltration, and (D) reduced colon length at PID3, n=6-7 per group. **E-F.** Pelvic irradiation impaired the intestinal barrier functionality, as shown by (E) bacterial counts in mesenteric lymph nodes and (F) reduced claudin-5 tight junction proteins from PID3 onwards, n=6-7 per group. *p <0.05, **p<0.01 by linear modelling. PID=post-irradiation day

▼ **Figure 2. Pelvic irradiation impacts diversity of gut microbiome in a delayed fashion**
NMDS plot of unweighted UniFrac beta analysis (representing the diversity between samples without consideration of relative abundances) showed that samples of irradiated mice collected at PID3 and PID7 clustered differently compared to the PID0 samples (PID0 vs PID1 p=0.858; PID0 vs PID3 p=0.025; PID0 vs PID7 p=0.004 by AMOVA), n=7 per group. PID=post-irradiation day



Conclusion and perspectives



▲ **Figure 3. Unprecedented findings showed how pelvic irradiation drives morphological and inflammatory implications, functionally impairing the intestinal barrier, which secondarily results in a microbiome shift**
The presented *in vivo* irradiation-gut-microbiome test platform allows further research on the pathobiology of pelvic irradiation-induced intestinal injury and resultant dysbiosis, as well as the exploration of potential mitigating treatments including drugs and food supplements.

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