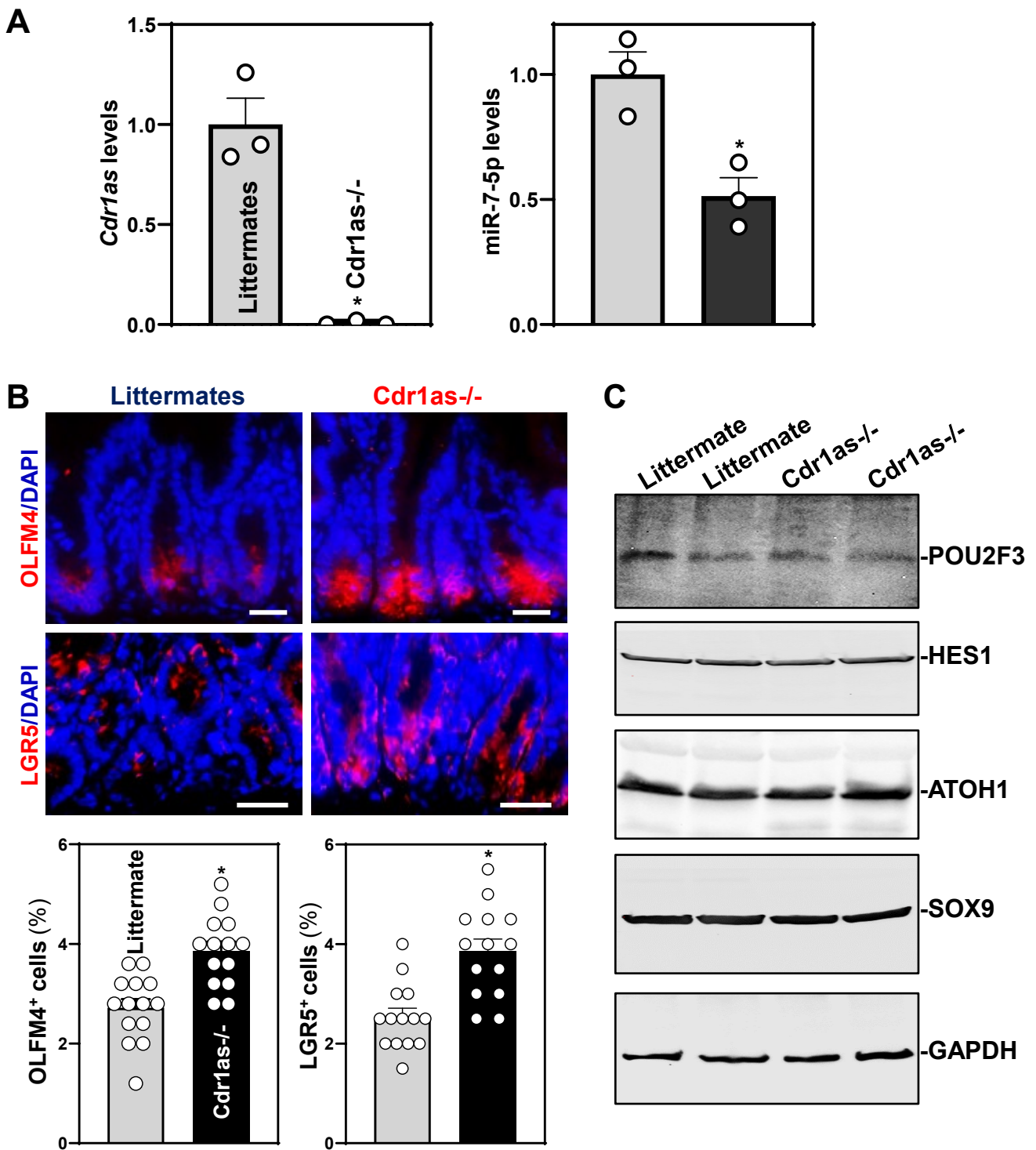
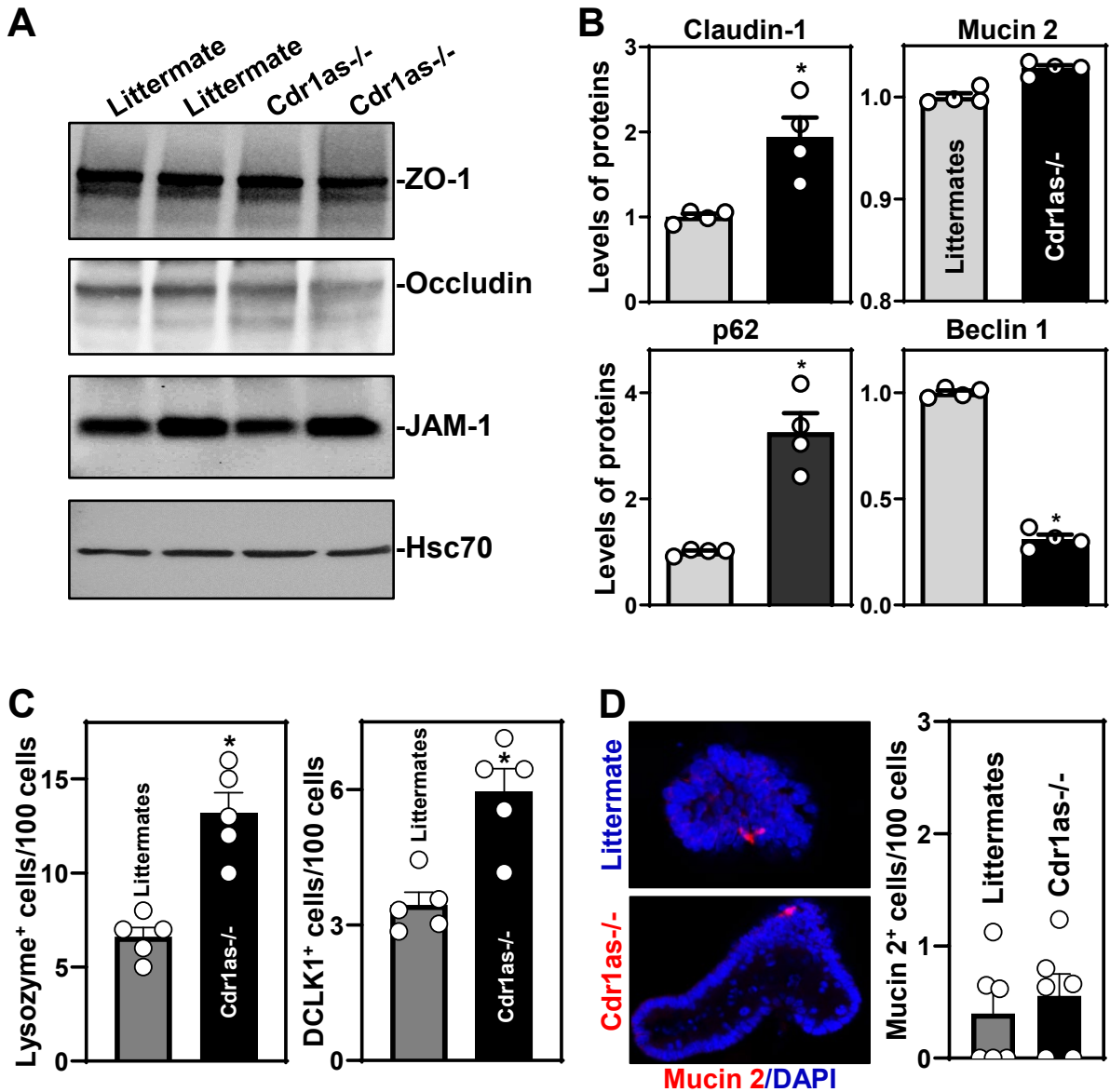


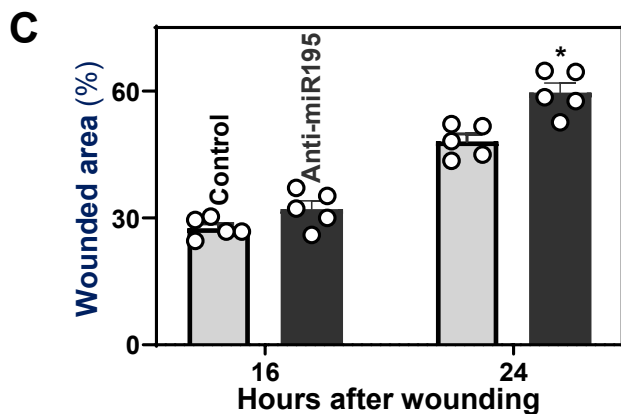
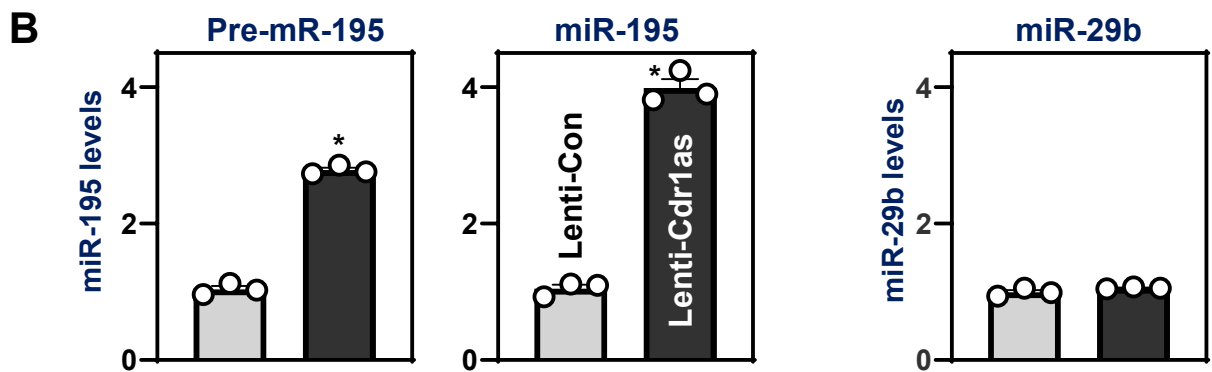
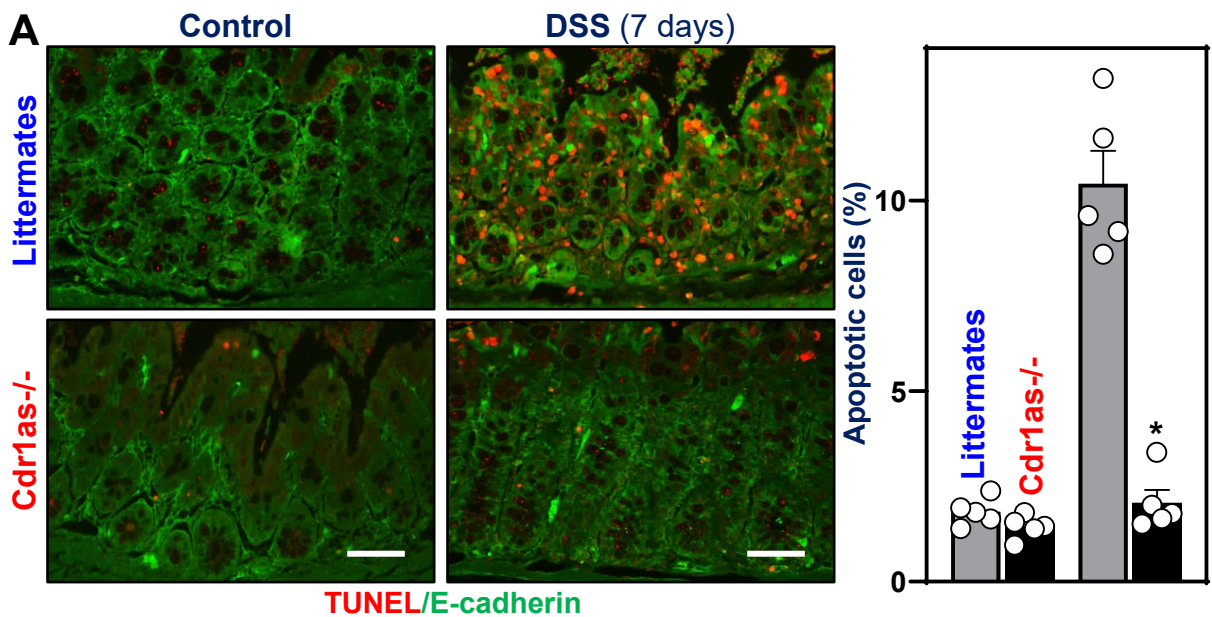
Supplementary Figure 1. Generation of *Cdr1as* knockout mice by CRISPR-Cas9. **(A)** The *Cdr1as* locus that was deleted. **(B)** PCR results from *ex vivo* validation in embryos microinjected with sgRNA and Cas9 enzyme. **(C)** DNA sequences of embryo microinjected with sgRNA #2 and #5. Green: sgRNA target; $\Delta-$: deleted mutation; $\Delta+$: insertional mutation. **(D)** Genotyping analysis showed that there were 21 *Cdr1as* knockout (KO) mice from total 44 mice generated by CRISPR-Cas9 technique. **(E,F)** Mouse, body weights, and gastrointestinal gross in littermate and *Cdr1as*^{-/-} mice ($n = 5$).



Supplementary Figure 2. (A) Levels of *Cdr1as* and miR-7-5p in the brain tissues of littermate and *cdr1as*^{-/-} mice as measured by Q-PCR assay. Values are the means \pm SEM ($n = 3$). * $P < 0.05$ compared with littermates. (B) Changes in ISC activity in the small intestinal mucosa after *Cdr1as* deletion, as examined by immunohistochemistry staining. ISCs were marked by OLFM4 (top) and LGR5 (bottom). scale bar: 25 μ m. * $P < 0.05$ compared with control littermates ($n = 10$). (C) Immunoblots of POU2F3, HES1, ATOH1, and SOX9 in the small intestinal mucosa of littermate and *Cdr1as*^{-/-} mice. Three separate experiments were performed and showed similar results.



Supplementary Figure 3. (A) Immunoblots of ZO-1, occludin, and JAM1 in the small intestinal mucosa of littermates and Cdr1as^{-/-} mice. Three separate experiments were performed and showed similar results. (B) Quantitative analysis derived from densitometric scans of immunoblots of claudin-1, mucin 2, p62, and beclin 1 in the small intestinal mucosa described in Figure 3A. Values are the means \pm SEM ($n = 4$). * $P < 0.05$ compared with control littermates. (C) Quantitative data of lysozyme-positive cells (left) and DCLK1-positive cell (right) in intestinal organoids described in Figure 4E,F. * $P < 0.05$ compared with the organoids generated from littermate mice ($n = 5$). (D) Goblet cells (marked by mucin 2) in intestinal organoids as described in Figure 4E. Values are the means \pm SEM ($n = 6$)



Supplementary Figure 4. (A) Apoptotic cells in the colonic mucosa of littermate and *Cdr1as*^{-/-} mice treated with 3% DSS in drinking water for 7 days (DSS), as measured with TUNEL staining. scale bar: 25 μ m. Values are means + SEM ($n = 5$). * $P < 0.05$ compared with littermates. **(B)** Levels of pre-miR-195, miR-195, and miR-29b in Caco-2 cells 72 h after infection with the lentiviral *Cdr1as* expression vector (Lenti-*Cdr1as*) or control lentiviral vector (Lenti-Con) as measured by Q-PCR. Values are the means \pm SEM ($n = 3$). * $P < 0.05$ compared with Lenti-Con. **(C)** Summarized data of epithelial repair after wounding in cells treated with lenti-Con alone or lenti-Con plus anti-miR195. * $P < 0.05$ compared with Len-Con alone ($n = 5$).