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IL-33 promotes gut mucosal wound healing by inducing miRNA-320 to stimulate epithelial restitution and repair

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Disclosure of Conflicts of Interest:

Conflict of interest : speaker for Sanofi, Angelini.

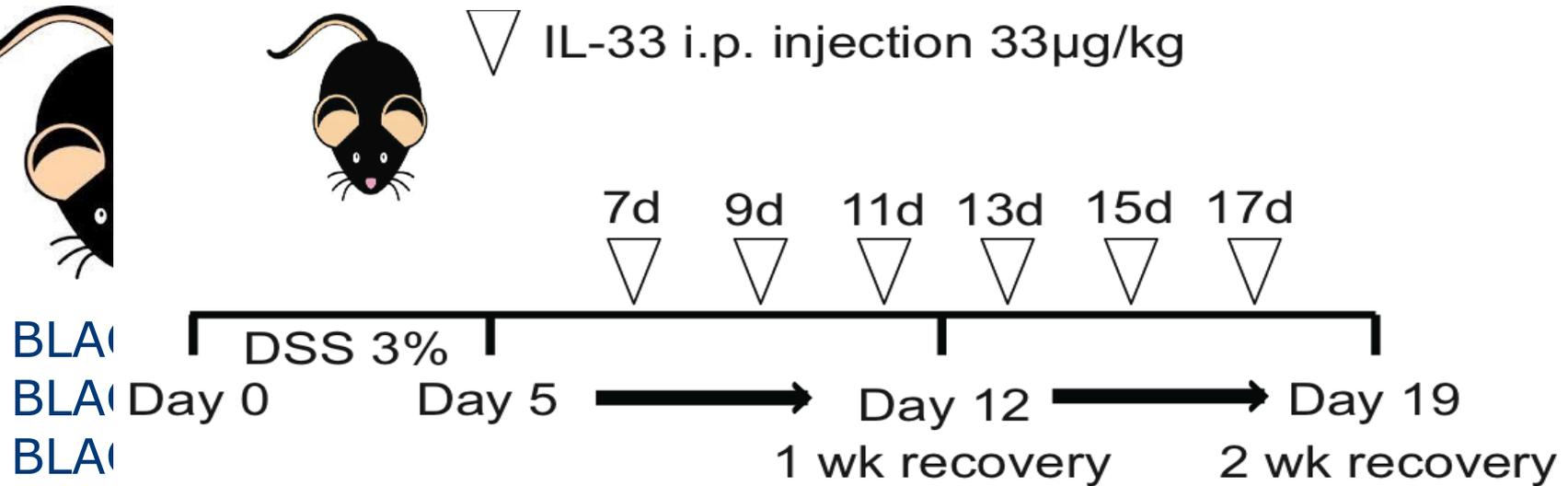
IL-33

- **First known as “nuclear factor from high endothelial venules” (NF-HEV), is a new member of the IL-1 cytokine family known to promote Th2 responses**
- Expression in non-hematopoietic and hematopoietic compartments
- Prototypic “alarmin”, passively released upon cellular damage, stress, or necrosis
- Signals local, innate immune responses
- Exogenous administration of IL-33 induces:
 - Eosinophilia
 - Splenomegaly
 - Goblet cell hyperplasia and mucus production
 - Increased serum levels of IL-5 and IgE
 - Epithelial proliferation

AIM

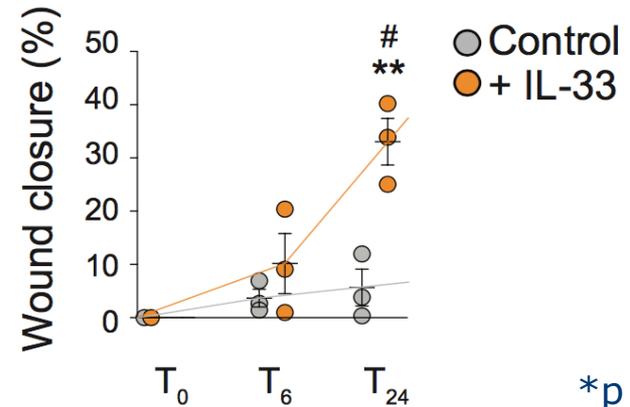
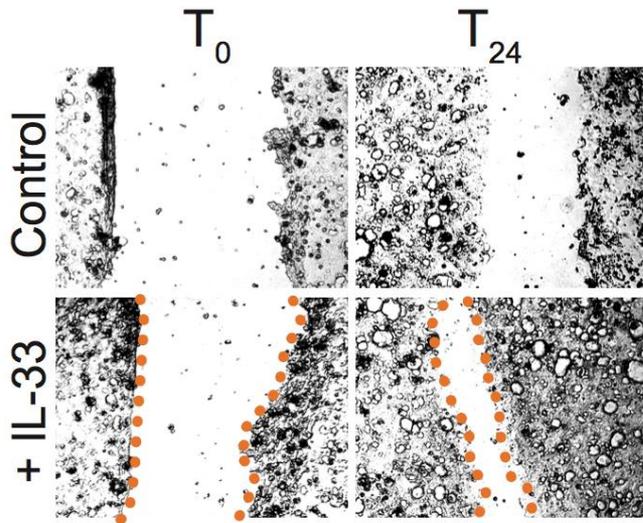
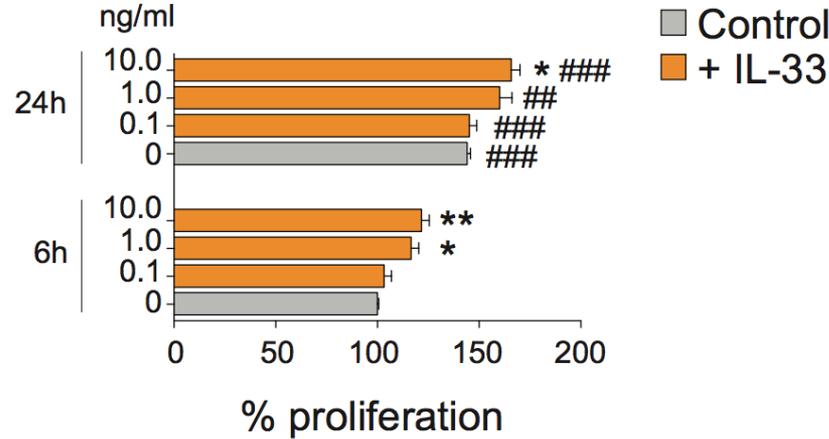
To characterize the role of the IL-33/ST2 axis following acute epithelial injury and mucosal repair in DSS-induced colitic mice.

METHODS



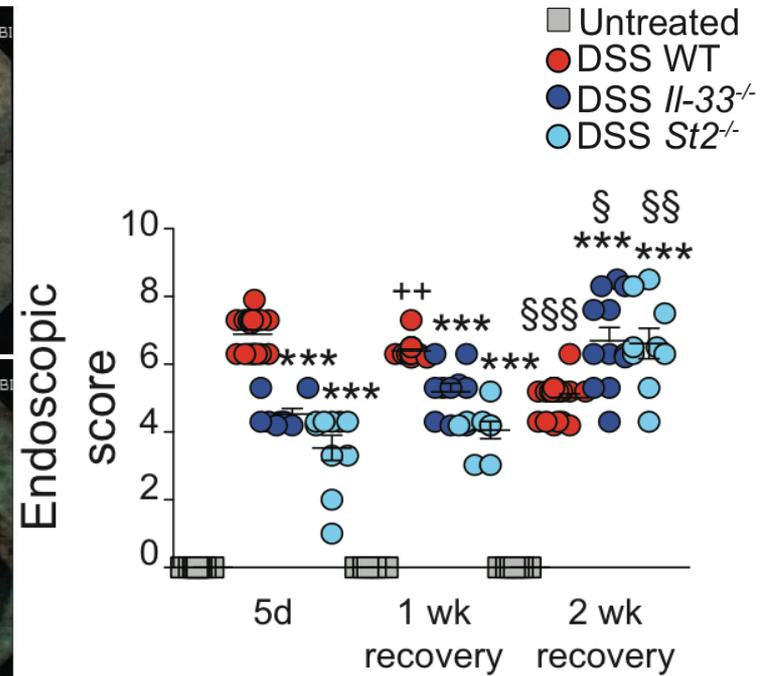
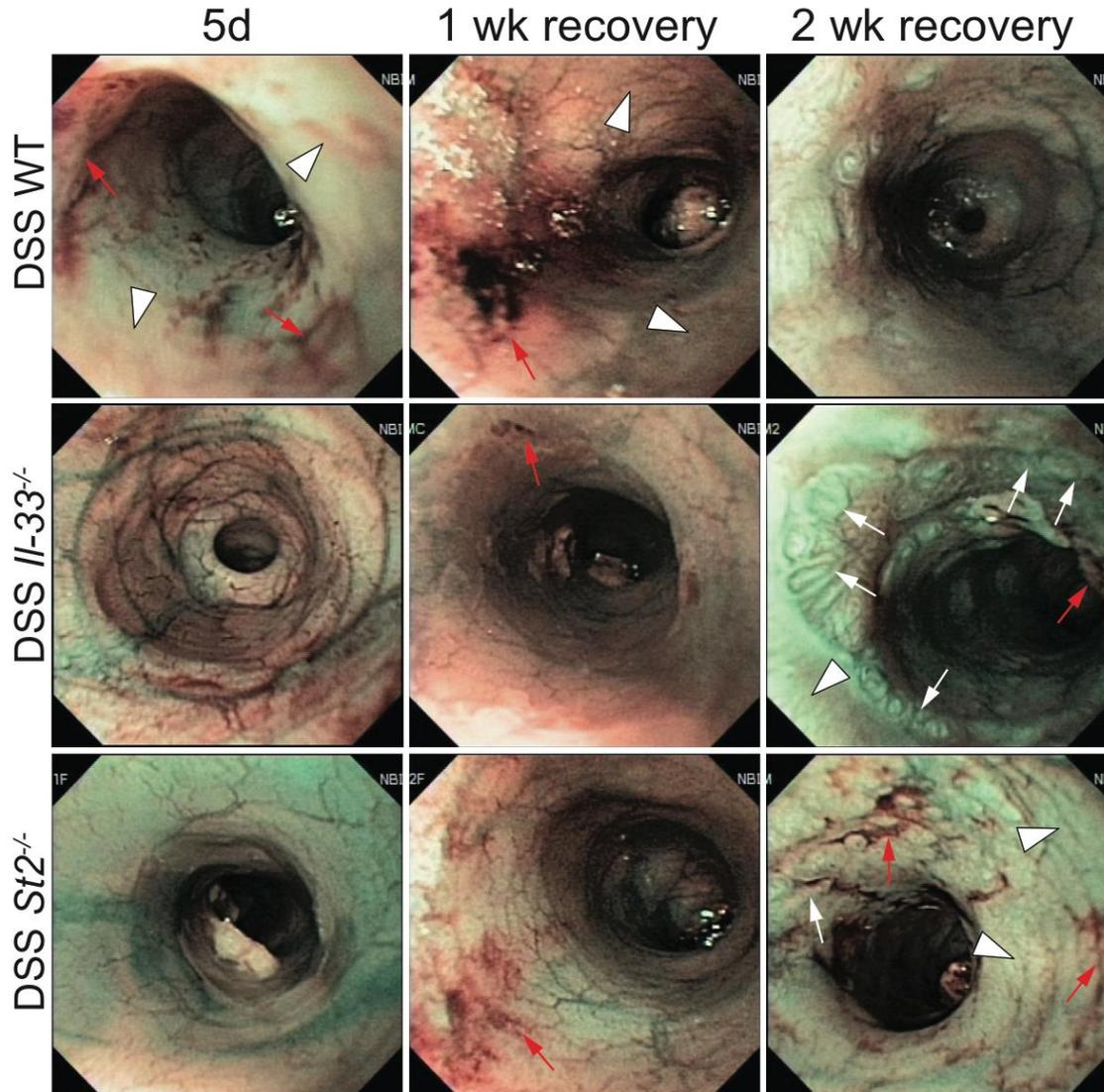
- Daily assessment of DAI and body weight loss
- Endoscopic and histologic evaluation at day 5, 12, 19
- qPCR for IL-33/ST2 mRNA expression on full-thickness colons
- IHC for IL-33/ST2 protein localization
- Gene array, IPA analysis and qPCR on Caco-2 IL-33 stimulated cells (100 ng/ml for 6h)
- MIR320 was selectively knocked-down through reverse transfection in Caco-2 cells.
- Cell proliferation by XTT assay and scratch assay

IL-33 induces cell proliferation and wound healing *in vitro*



n ≥ 3
 *p < 0.05
 **p < 0.01
 ***p < 0.001

IL-33/ST2 deficiency blocks epithelial repair and mucosal healing after two weeks of recovery following DSS challenge



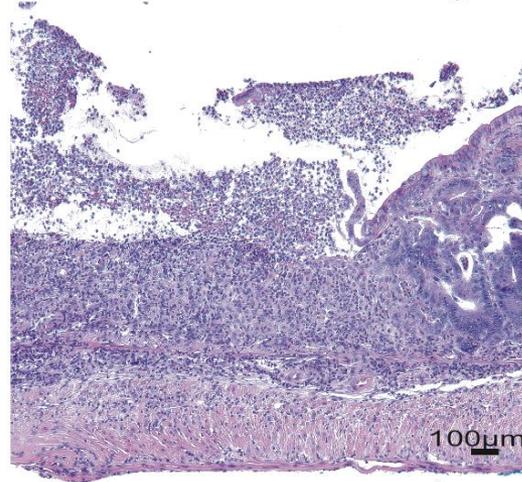
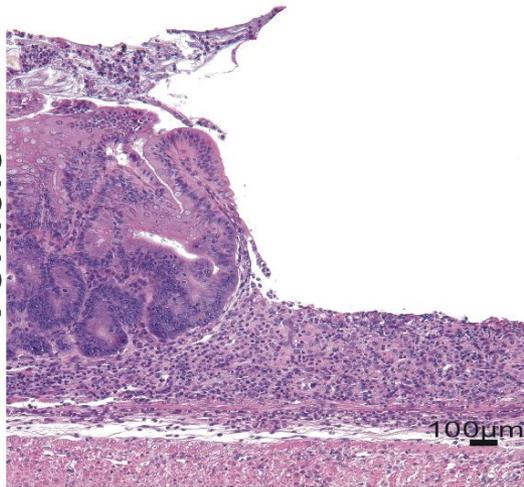
* $p < 0.05$
 ** $p < 0.01$
 *** $p < 0.001$

Exogenous IL-33 administration during recovery induces intestinal mucosal healing after DSS challenge and decreases colonic inflammation

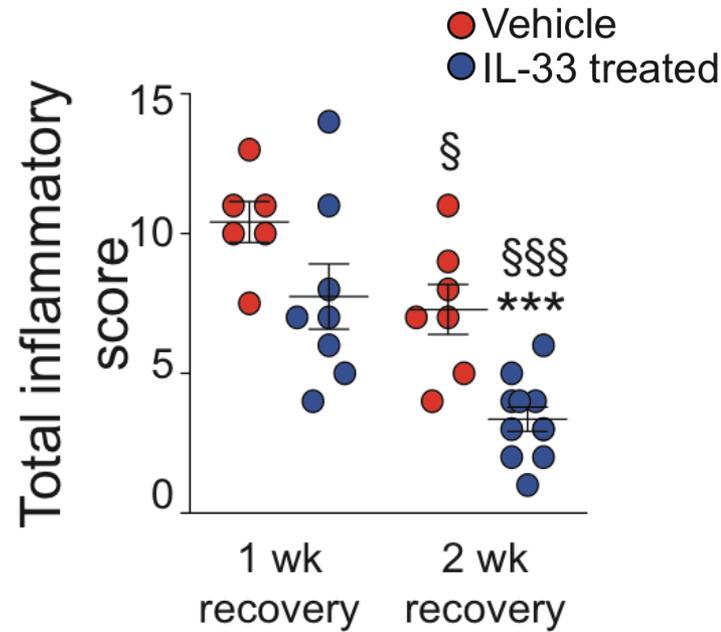
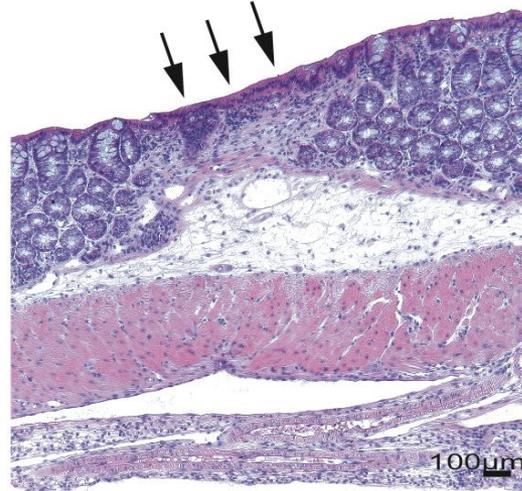
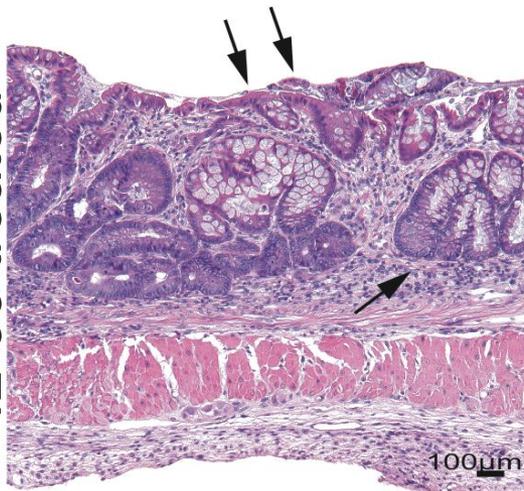
1 wk recovery

2 wk recovery

Vehicle

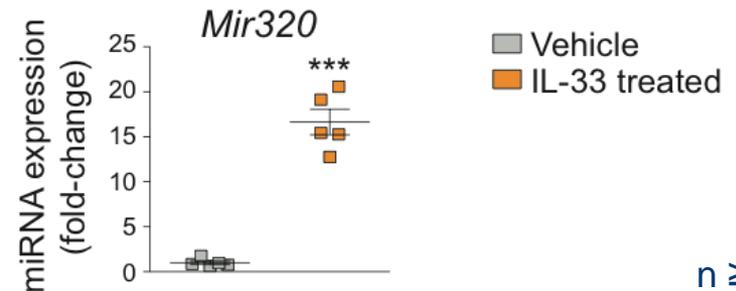
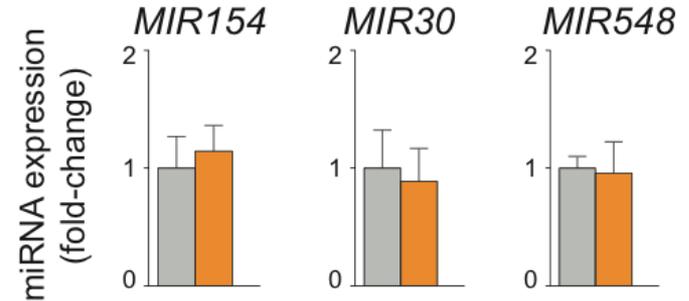
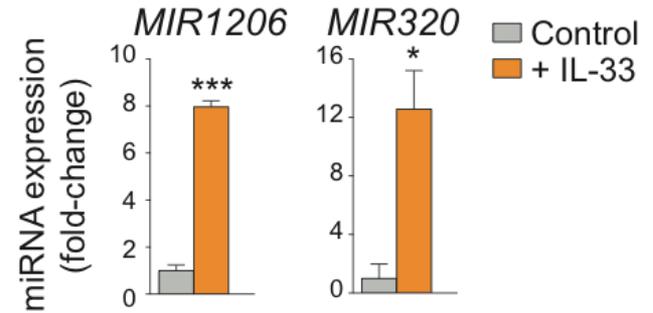
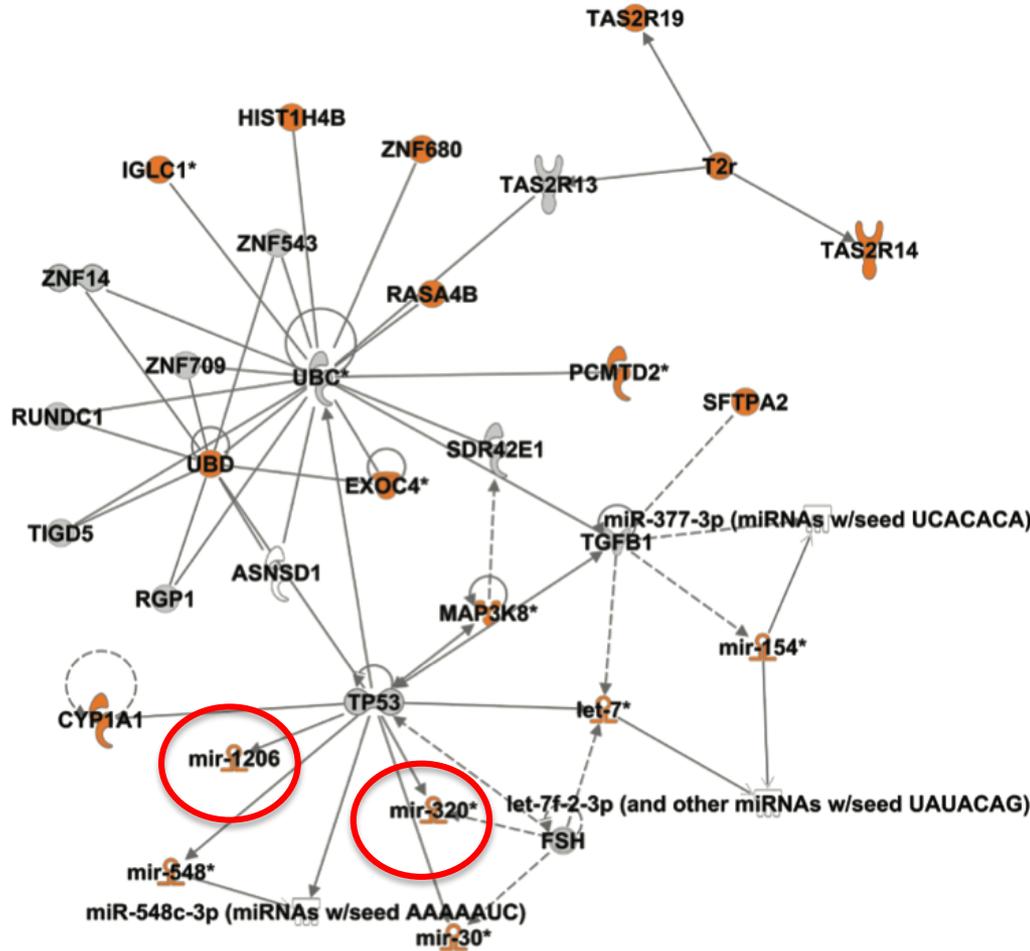


IL-33 treated



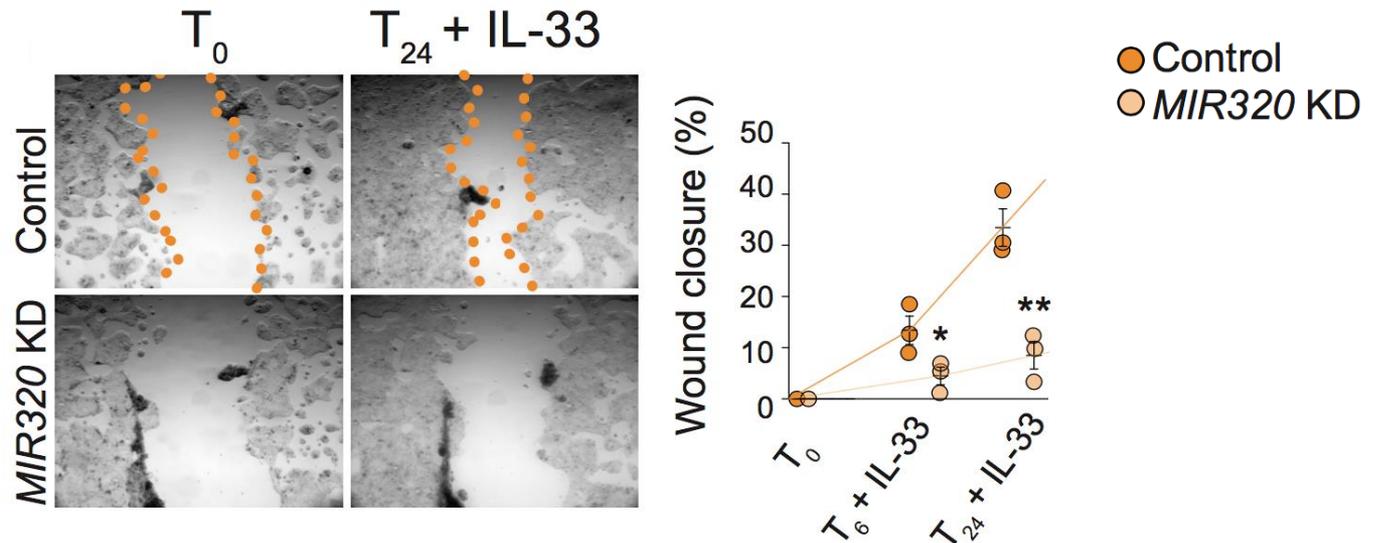
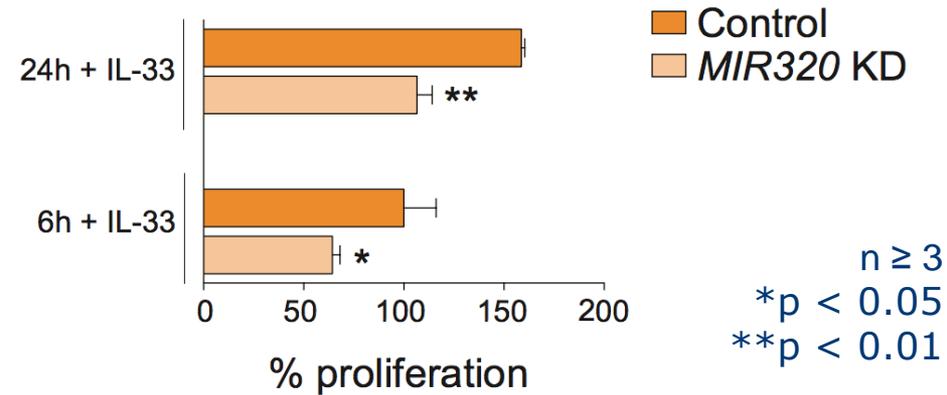
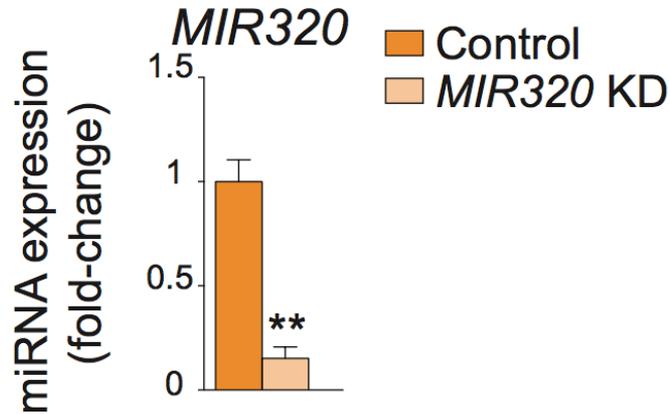
*p < 0.05
 ***p < 0.001

IL-33 upregulates specific miRNAs involved in cell proliferation and repair



n ≥ 3
 *p < 0.05
 ***p < 0.001

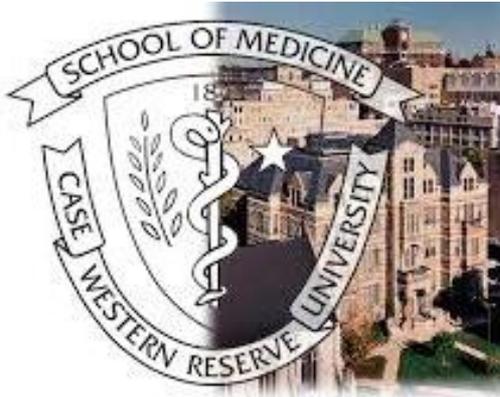
miRNA-320 knockdown downregulates IL-33-induced cell proliferation and wound healing



SUMMARY

- ✓ Our results suggest that during acute, resolving colitis, the IL-33/ST2 system plays a critical role in gut mucosal wound healing by inducing epithelial-derived miRNA-320 that promotes epithelial restitution and restoration of barrier integrity.
- ✓ IL-33 appears to follow the trend of several innate-type cytokines, including members of the IL-1 family (*i.e.*, IL-1 α , IL-1 β , and IL-18), that possess dichotomous functions of inducing potent proinflammatory responses, while also promoting protection and the return to immune homeostasis.
- ✓ On the base of these data, future therapeutical protocols will need to consider the specific immunological status of the host, and the typology and phase of the intestinal inflammatory process with the end goal of promoting gut health.

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