# IL-33 Induces Genes Involved in Epithelial-Mesenchymal Transition in Intestinal Epithelial Cells

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## Introduction
IL-33 is induced in the mucosa of adult and pediatric patients with inflammatory bowel disease. IL-33 has been found to have an indirect role in intestinal epithelial differentiation into goblet cells by inducing IL-13 production from group 2 innate lymphoid cells and T helper 2 cells. However, how IL-33 directly affects epithelial function remains unknown.

## Hypothesis
IL-33 directly induces genes involved in epithelial-mesenchymal transition (EMT) in intestinal epithelial cells.

## Methods
Colonoids, 3-dimensional primary cultures that contain all types of colon epithelial cells, were generated from mouse colon crypts. RNA sequencing was performed on colonoids exposed to IL-33 for 0, 2, or 6 hours. RT-PCR for the housekeeping gene *Gapdh* and the EMT genes *Cdh2*, *Zeb1*, and *Igfbp5* was performed on colonoids exposed to IL-33 for 0, 2, 6, or 24 hours. WT and IL-13–/– mice were given intraperitoneal injections of IL-33. IL-13–/– mice were utilized since IL-13 is known to be induced by IL-33 and act on epithelial cells. Whole colon tissue and colon epithelial cells were isolated and underwent RT-PCR for *Gapdh*, *Cdh2*, *Zeb1*, and *Igfbp5*.

## Results
RNA sequencing of colonoids exposed to IL-33 revealed upregulation of *Cdh2*, *Zeb1*, and *Igfbp5*, three genes involved in EMT. RT-PCR showed a trend toward increase in all three genes. To explore the role in vivo, whole colon tissue and epithelial cells were isolated from WT and IL 13–/– mice treated with IL-33 for 4 days. No changes were seen in these genes in WT whole tissue. In WT epithelial cells, we saw a slight increase in *Cdh2* and slight decreases in *Zeb1* and *Igfbp5*, suggesting indirect effects of IL-33 may be affecting gene expression in vivo. In IL 13–/– total tissue, we saw a significant increase in *Cdh2* and *Zeb1* and an increase in *Igfbp5*. However, in isolated epithelial cells all genes were decreased, indicating effects of IL-33 on other cell types.

## Conclusions
IL-33 can directly affect intestinal epithelial cells by increasing the expression of genes involved in EMT, specifically *Cdh2*, *Zeb1*, and *Igfbp5*. These results can be seen in vitro but may be overcome in vivo by secondary effects of IL-33.

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