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CAG-IBD Precision medicine in Inflammatory bowel disease

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UTILIZING PATIENT-DERIVED COLON ORGANOIDS TO EXPLORE THE EFFECT OF GENETICALLY DETERMINED ERAP2-PROFICIENCY UPON PROINFLAMMATORY STIMULATION

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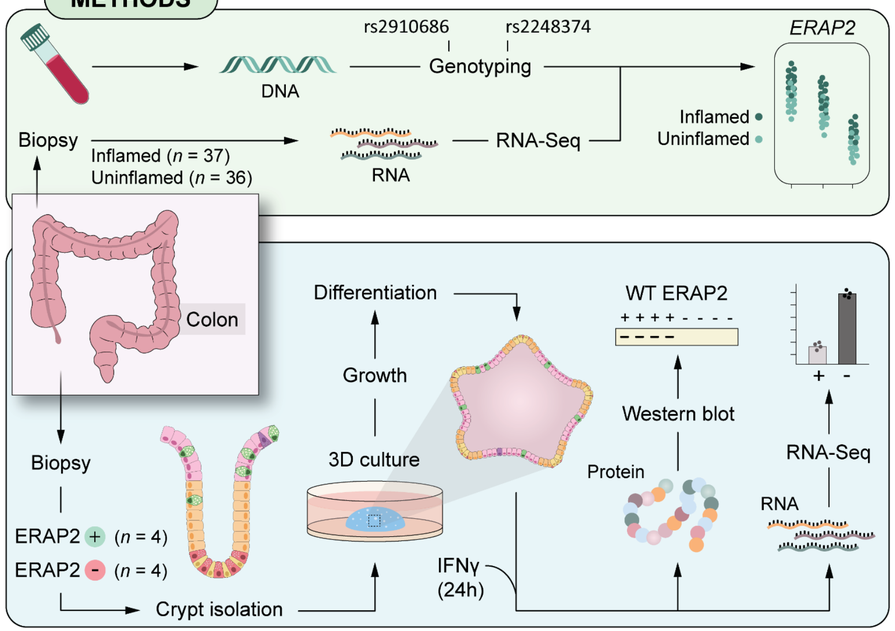
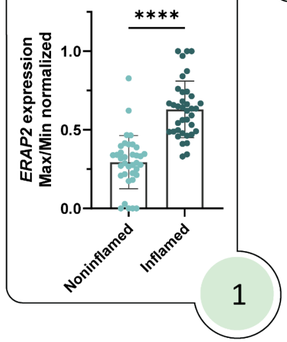
BACKGROUND

A positive family history of inflammatory bowel disease (IBD) remains the strongest risk factor for development of disease, underpinning genetic factors in IBD etiology. Genetic variants in Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) have been associated with numerous inflammatory conditions, including IBD. How ERAP2 contribute to IBD pathogenesis is however unresolved. As the epithelial involvement in IBD pathogenesis is getting increasingly recognized, we set out to explore the impact of epithelial ERAP2 presence upon inflammatory encounter using human-derived colonoids as a model system. To investigate the effect of genotype on ERAP2 expression in different disease states, patient material from a IBD cohort was used to correlate genotype to ERAP2 expression in inflamed and noninflamed colonic biopsies.

METHODS



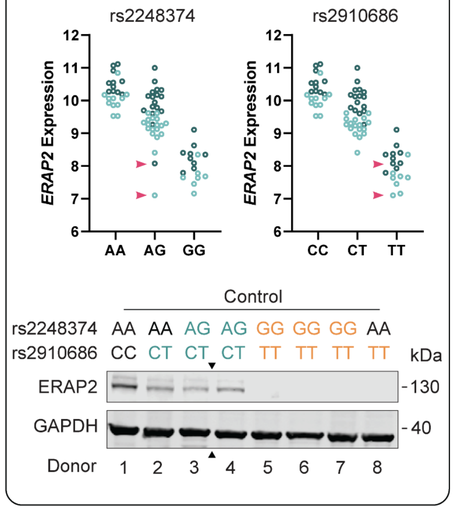
RESULTS



1

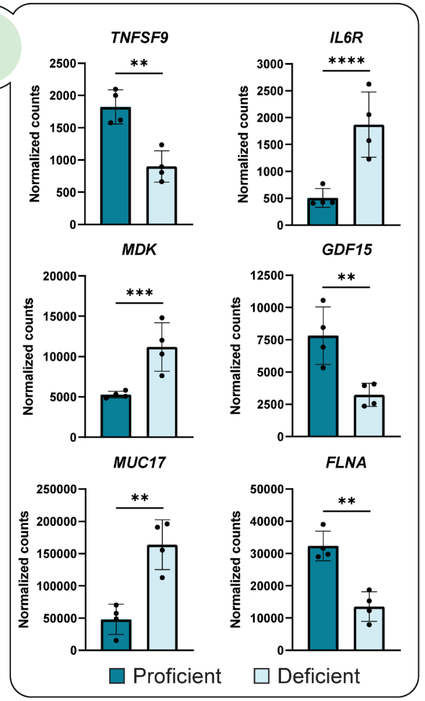
Colonic *ERAP2* expression is increased in active IBD. Within each rs2910686 genotype, expression levels were max/min normalized to correct for genotype effect on expression levels. An unpaired t-test was used to compare noninflamed and inflamed colonic samples ($P < 0.0001$).

2



Mechanisms independent of rs2248374 can lead to ERAP2-deficiency. Top panel: *ERAP2* expression for rs2248374 (A/G) and rs2910686 (C/T) in inflamed ($n = 37$, dark green) and noninflamed ($n = 36$, light green) pinch biopsies across genotype. Expression is presented as log2 transformed, normalized counts. Red arrows indicate samples where rs2248374 and rs2910686 are discordant. Bottom panel: Verification of ERAP2-proficient and deficient donors. Genotype for rs2248374 and rs2910686 indicated for each donor. Donor 8 (rs2248374 AA, rs2910686 TT) does not express detectable ERAP2 protein.

3



ERAP2-proficient and -deficient colonoid donors display differential expression 24h post IFNγ stimulation. A total of 586 genes were differentially expressed between the two groups, including genes encoding proteins with regulator activity (*TNFSF9, MDK, GDF15, ILR6A, FLNA*) and the extracellular matrix structural constituent *MUC17*.

CONCLUSIONS

1. *ERAP2* is differentially expressed in active IBD mucosa when taking rs2910686 genotype into account
2. Mechanisms independent of rs2248374 can lead to ERAP2-deficiency
3. ERAP2 rs2910686 genotype affects expression level of related genes upon proinflammatory stimulation
4. Through genotype-based stratification of colonoid donors, we demonstrate that organoids act as a useful and physiologically relevant model system for evaluating the effects of disease-associated SNPs

This work was recently published in *Journal of Translational Medicine:*
Sæterstad, S., Østvik, A. E., Hansen, M. D., Bruland, T., & van Beelen Granlund, A. (2024). The effect of rs2910686 on ERAP2 expression in IBD and epithelial inflammatory response. *Journal of Translational Medicine*, 22(1), 750.

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