Presentation P008

Machine Learning Derived Histological Features of Epithelial Injury and Repair in Ulcerative Colitis Biopsies Correlate with Disease Severity

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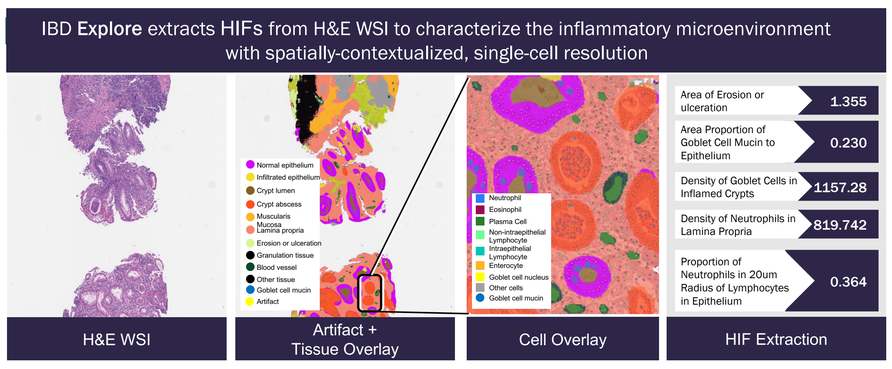
BACKGROUND

Ulcerative colitis (UC) is an incurable chronic and debilitating disease. Frequent relapse is common despite available therapeutics. Endoscopically and histologically confirmed mucosal healing is the gold standard for long term remission, but a better understanding of disease pathology is needed for all patients to achieve inflammation reduction plus epithelial repair and wound healing. Here, we describe machine learning (ML) models that exhaustively quantify the inflammatory and epithelial histologic morphology of the colonic mucosa. Model-derived features are associated with Geboes Score (GS).

METHODS

ML models (IBD Explore™, PathAI, Boston[1]) previously trained to quantify tissue features (e.g. epithelium) and cells (e.g. lymphocytes) were deployed on 447 whole slide images (WSI) of hematoxylin and eosin (H&E)-stained UC colonic mucosa from clinical and commercial sources.

FIGURE 1. HIF Extraction from ML Models



Model predictions yielded >900 quantitative human interpretable features (HIFs; **Figure 1**). To identify histological features of epithelial injury and repair, further analyses focused on only HIFs that are relevant to epithelial structure and composition (**Table 1**).

Slide-level GS (subgrades and Grade Level) were assigned to each WSI based on a median consensus score of three expert gastrointestinal pathologists. Absolute Spearman rank correlations between individual HIFs and GS were calculated and associations between HIFs and GS were assessed at the FC level.

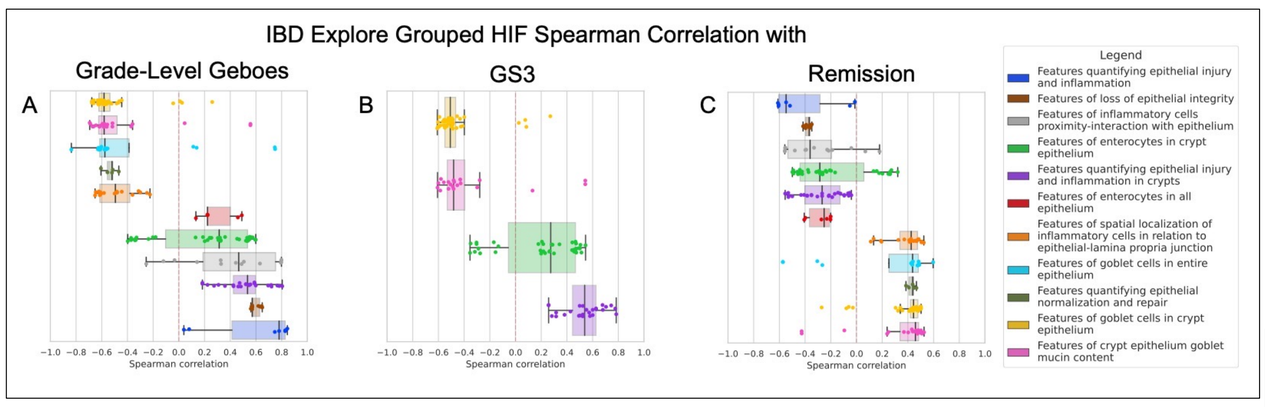
Feature category	Human interpretable feature	Spearman
Goblet cells in entire epithelium features	Area proportion of goblet cell mucin over infiltrated epithelium	-0.84
Crypt epithelium goblet mucin content features	Median area proportion of goblet cell mucin over all epithelium across inflamed crypts	-0.69
Goblet cells in crypt epithelium features	Mean density of goblet cells in epithelium across inflamed crypts	-0.68
Spatial localization of inflammatory cells in relation to epithelial-lamina propria junction features	Count proportion of non-intraepithelial lymphocytes within a 40 um radius of goblet cells over non-intraepithelial lymphocytes	-0.65
Epithelial normalization and repair features	Area proportion of normal epithelium over mucosa	-0.61
Enterocytes in all epithelium features	Count proportion of enterocytes over all cells in normal epithelium	0.49
Enterocytes in crypt epithelium features	Median count proportion of enterocytes over all cells in all epithelium across inflamed crypts	0.60
Loss of epithelial integrity features	Area proportion of erosion/ulceration over mucosa	0.65
Inflammatory cells proximity-interaction with epithelium features	Ratio of the total number of neutrophils within 40 um radius of enterocytes over all epithelium	0.80
Epithelial injury and inflammation in crypts features	Mean count proportion of neutrophils to all cells in crypt epithelium across all crypts	0.80
Epithelial injury and inflammation features	Area proportion of infiltrated epithelium over all epithelium	0.84

TABLE 1. 212 HIFs were divided into 11 feature categories (FC) based on whether they describe loss of integrity, total or crypt injury and repair; the individual HIF from each FC with the strongest correlation to Grade Level GS is shown.

RESULTS

HIFs were assessed at the FC level to identify broad trends associated with GS. Goblet cell HIFs in all epithelium and in crypt epithelium had the strongest associations and were negatively correlated with disease activity (**Figure 2**).

FIGURE 2. Correlations between HIF FCs Grade-Level GS, GS3, and remission reveal significant positive associations between (A) enterocyte and epithelium injury features with grade-level GS, (B) between epithelial injury in the crypts and GS3, and (C) goblet cells in the epithelium and crypts, and goblet cell mucin in the crypt epithelium with remission. (B) Conversely, GS3 was significantly negatively correlated with goblet cells in the crypt epithelium and goblet cell mucin in the crypt epithelium.



Subgrade 3 GS was most strongly, and positively, correlated with epithelial injury and repair in the crypts, and negatively correlated with goblet cells in crypt epithelium and crypt epithelium goblet cell mucin (**Figure 2B**).

Model overlay outputs allow direct visualisation of histological features (**Figure 3**).

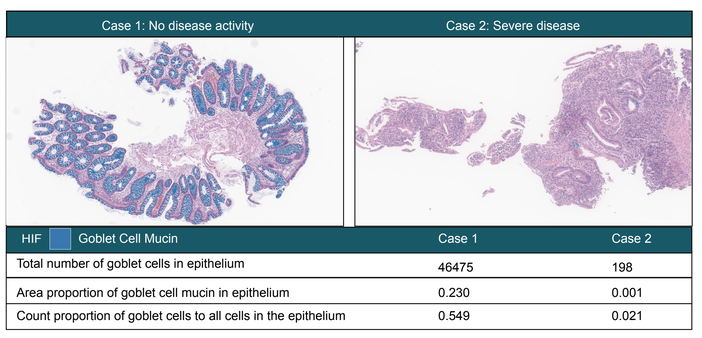
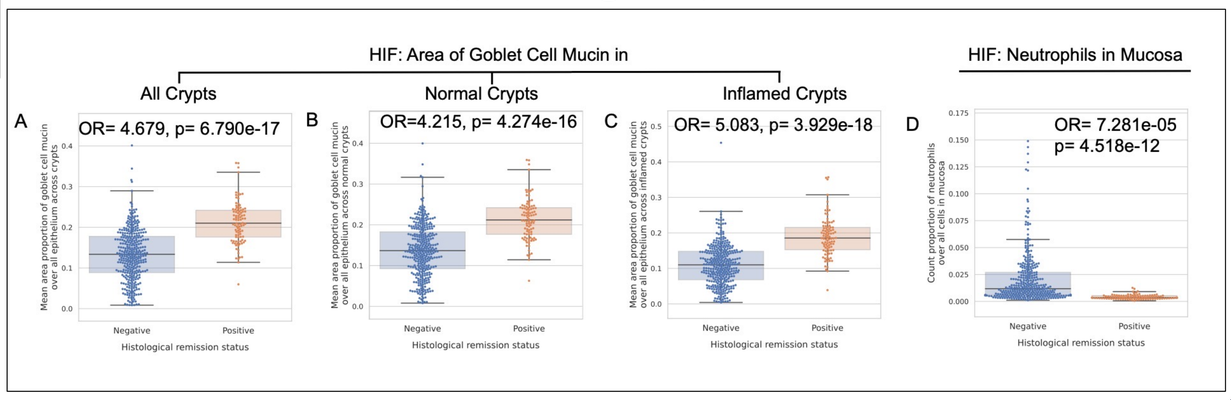


FIGURE 3. Goblet cell mucin predictions shown as overlays on two different H&E-stained WSI cases of no disease activity and severe disease activity, and values of related HIFs.

Histologic differences between remission and non-remission were explored using HIFs. Marked loss of goblet cell mucin and decrease in related HIFs was shown in tissue with severe disease compared to tissue with no disease activity (**Figure 3**). Significant increases in the area proportion goblet cell mucin in crypts were found in cases of remission, whether all crypts were included (**Figure 4A**) or only normal crypts (**Figure 4B**), or only inflamed crypts (**Figure 4C**). Higher abundance of neutrophils was associated with non-remission (**Figure 4D**).

FIGURE 4. Values of HIFs describing goblet cell mucin and neutrophile density tissue from patients that achieved remission (orange, positive) and patients that did not (blue, negative).



CONCLUSIONS

Quantitative HIFs describing mucosa epithelial injury and repair strongly correlate with GS, and specifically HIFs that quantify goblet cell mucin correlate with histologic remission. Our models produce a granular, measurable blueprint of the epithelium that can be leveraged to inform multiple hypotheses for target selection, mechanism of action, and disease activity.

AUTHOR DISCLOSURES
M.G., Y.Z., C.S., J.S., J.K.,V.M., K.S., M.T., C.J., and F.N. are all employees of and stockholders in PathAI

[1] IBD Explore is for research use only. Not for use in diagnostic procedures.

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