Introduction:

Several transcriptional signatures have been published that predict anti-TNF resistance in ulcerative colitis (UC). However, little is known about the molecular mechanisms underpinning this and how they relate to other therapies.

Methods:

Transcriptional profiles of colonic biopsies taken before treatment for moderate-to-severe UC were analysed from Gene Expression Omnibus. Patients were subsequently treated with infliximab (n = 24 and n = 22), golimumab (n = 84) and ustekinumab (n = 358). Molecular pathways from the Reactome database that were differentially enriched between those who did and did not achieve mucosal healing during induction were found and shared pathways between cohorts were noted. The largest cohort was used to correlate enrichment of published resistance signatures in actively inflamed mucosa. Hierarchical clustering was then performed for non-responders to identify transcriptomic similarities. Analyses were performed on R 4.2.2 (Vienna).

Results:

Many biological pathways were associated with resistance across the cohorts (1079 pathways, adjusted p value < 0.01). Sixty pathways were shared between 3 or 4 datasets. Extracellular matrix (ECM) dysregulation, neutrophil degranulation and interleukin signalling were most prominent. Further analyses revealed that proteins forming these pathways interact *in vivo* within a discrete, closely intertwined functional network. The enrichment of published transcript signatures in inflamed mucosa correlated highly. For instance, correlation between enrichment of UC1 (Czarnewski et al, 2019) and M5 (Friedrich et al 2021) was 0.96. Over-representation analyses showed that these signatures represent processes such as interleukin signalling and neutrophil activity. Hierarchical clustering of non-responders revealed two distinct groups: those with high (NRhi) and low (NRlo) signature enrichment. Cellular deconvolution analyses showed that neutrophils are more prevalent in NRhi compared to NRlo and that eosinophils may be more frequent in NRlo than NRhi patients (Figure 2).

Conclusions:

ECM dysregulation and neutrophil activity may underlie a core ‘resistome’ that heralds poor treatment outcomes to anti-TNFs and ustekinumab. Supporting this, enrichment scores of published transcript signatures in inflamed tissue correlate highly, suggesting many of these represent shared, or similar, mechanisms of resistance. However, there is a separate resistant cohort with different molecular drivers. This has important implications for precision medicine in UC.