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Review

From single-target to cellular niche targeting in Crohn's disease: intercepting bad communications

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ABSTRACT

The mainstay of moderate to severe Crohn's disease (CD), anti-TNF treatment, shows no clinical benefit in ~40% of patients, likely due to incomplete cellular targeting and delayed treatment institution. While single-target therapeutics have been highly effective for some CD patients, substantial limitations with respect to safety, efficacy, and long-term, complete remission remain. Deconvolution of the cellular and molecular circuitry of tissue lesions underscores the importance of combinatorial strategies targeting cellular niches. This review aims to evaluate current therapeutic approaches used to manage CD, and highlight recent advances to our cellular, genetic, and molecular understanding of mechanisms driving pathogenic niche activation in CD. We propose new frameworks outlining that combinatorial therapies, along with serial tissue sampling and studies guided by genetics and genomics, can advance on current treatment approaches and will inform newer strategies upon which we can move towards precision therapeutics in IBD.

1. Introduction

Crohn's disease (CD) is a complex, chronic inflammatory intestinal disease, driven by aberrant genetics, environmental, and host immune factors. Owing to the complex etiology of CD, therapeutic strategies maximizing benefit to most patients is currently unavailable [1]. The mainstay of moderate to severe Crohn's disease, anti-TNF treatment, shows no clinical benefit in ~40% of patients, reflecting continued activation of untargeted cell modules and pathways [2–4]. Many of the hundreds of independent risk loci associated with CD risk [5] are expressed by immune, stromal, and epithelial cells, revealing that polygenicity of disease takes phenotypic form involving many specialised cell types. Continued refinement of treatment strategies by incorporating these findings will be necessary, as we continue to elucidate precise cellular mechanisms that drive CD pathogenesis.

Besides cellular and molecular mechanisms of disease, GWAS have identified over 250 independent loci, which increase CD risk [5]. Many of these risk loci lie among genes involved in innate immune pathways, such as *NOD2, ATG16L1, STAT3,* and *IL23* family members [5]. Among these, it has long been established that the highest effect risk alleles in European ancestry CD are loss-of-function mutations in NOD2 [5], [6], also associated with an earlier age of disease onset, ileal location, and increased risk for fibrostenotic complications [7]. While associations between NOD2 mutations alone and anti-TNF response have not been reported [8], early treatment institution [9], in combination with tight control [10] of molecular responses may alter responses.

Here we present proposed systemic mechanisms of pathogenic niche regulation in Crohn's disease, underscoring the importance of cellular niches as therapeutic targets. We evaluate current therapeutics used to treat CD, and propose new frameworks guided by genomics and transcriptomic discoveries, upon which we can design therapeutic strategies that advance from single targets towards combinatorial, niche targeting.

2. Current therapeutics in Crohn's disease

While several agents have been available for the treatment and management of Crohn's disease, half of all patients develop intestinal complications within twenty years after diagnosis, and 50% of all patients require surgery within ten years after diagnosis [11]. Common agents used to treat and manage CD include biologics, thiopurines, antibiotics, and steroids, with frequent updates in clinical practice guidelines based on evidence of success in medical management of CD [12]. Traditional treatment approaches were based on a step-up approach, whereby patients would first be treated with anti-inflammatories, then with immunomodulators, and finally with biologic agents [13]. However, this approach has largely been reevaluated due to delays in achieving clinical remission, and inability to

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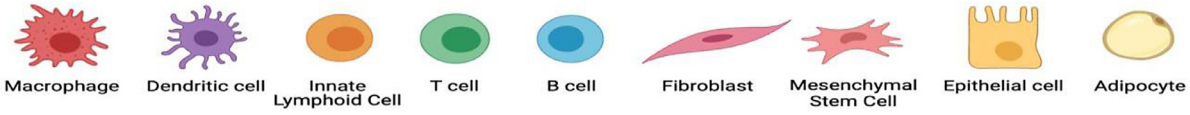
Table 1
Therapeutic strategies, cell targets, and disease activity of Crohn's disease management. Table to outline approved treatment strategies as suggested in the most recent ECCO Guidelines on therapeutics in Crohn's Disease[12], and to suggest some of the next class of potentially approved therapeutics.

Therapeutic	Approved?	Mechanism of Action	Cell targets	CD disease activity treated
Corticosteroid	Yes	Steroid; Anti-inflammatory		Mild to moderate
5-Aminosalicytates	Yes	Anti-inflammatory		Mild to moderate
Thiopurines/ 6-Mercaptopurine/ Methotrexate	Yes	Immunosuppression		Moderate to severe
Anti-TNF therapy	Yes	TNFa neutralization, apoptosis induction, inhibition of lymphocyte homing		Moderate to severe
Vedolizumab	Yes	A4b7 integrin blocker; inhibition of lymphocyte homing		Moderate to severe
Ustekinumab	Yes	Inhibition of p40 subunit of IL12 and IL23		Moderate to severe
JAK inhibitors	Tofacitinib for UC; Filgotinib (phase 3 clinical trials for CD)	JAK-STAT inhibition		Moderate to severe
RIPK2-inhibitors	No	RIPK2 inhibition		
S-1P inhibitors	No	Inhibition of lymphocyte migration		Moderate to severe
gp130 inhibitors: Olamkicept	No	Soluble gp130 inhibition; IL6 trans-signaling blockade	Soluble form found in circulation	
MSC transplantation	No	Mesenchymal Stem Cell transplant (administered into wall of perianal fistulizing tract)		Severe/fistulizing



personalise treatments that would be tailored to an individual's disease manifestation and underlying influences (e.g. genetics). More recent rethinking of treatment strategies has led to the "treat-to-target" approach, which aims to evaluate the most effective agent by identifying the appropriate target, followed by tight monitoring of treatment effects; the goal being to treat disease early and avoid ongoing chronic inflammation, which could lead to complications (such as strictures and fistulas), recurrence of disease post-surgery, and multiple hospitalisations [14]. Though specific guidelines to tailor personalised therapy aren't entirely outlined, disease location, disease severity, presence of complications, timing of treatment institution, and prior treatment failures are heavily evaluated. In particular, tight control of treatment outcomes at regular intervals is essential for ensuring that treatment strategies are tailored and adjusted to patient needs through disease trajectory [10].

2.1. Treatment of mild to moderate CD: remission induction

Inflammatory drugs such as 5-Aminosalicyates (5-ASAs) are commonly and effectively used for treatment in ulcerative colitis [15], but have shown more moderate clinical efficacy in CD patients [16]. Commonly used agents include mesalamine and sulfasalazine, showing benefit primarily in patients with Crohn's colitis [17]. Proposed mechanisms of action for 5-ASAs include inhibition of cyclooxygenase and prostaglandins [18], and induction of regulatory T cells [19]. Though there is limited clinical efficacy in 5-ASAs for CD treatment, we can still glean cellular and molecular targets (Table 1); while this may paint an incomplete picture, efficacy limits and cellular mechanisms could be useful considerations when developing combination therapies. Studies that have shown any clinical efficacy of 5-ASAs in CD patients are either restricted to colonic CD [20] or are inferior to corticosteroid treatment alone [17] or via combination [21]. Corticosteroids are also used in the treatment of both ulcerative colitis and Crohn's disease [22], and are particularly effective in CD patients when used for more than 15 weeks [23]; however corticosteroid use also presents with adverse side effects, shows limited endoscopic healing [24], and is not recommended for maintenance of remission [12,22]. In such instances, the use of appropriately dosed antibiotic agents are valuable options for inducing remission in patients with

mild to moderate Crohn's disease [25], especially for those patients who present with colonic CD.

2.2. Treatment of moderate-severe CD: Remission maintenance

Patients with moderate to severe Crohn's disease are commonly treated with immunosuppressives, such as methotrexate and thiopurines (Table 1). These have shown to be effective at both inducing mucosal healing [24] and maintaining remission [26], however discontinuation of medication due to adverse effects have also been documented [27]. Proposed mechanisms of these drugs include increasing T cell apoptosis [28], altering expression of adhesion molecules, and suppressing proinflammatory cytokine release [29]. Other lymphoid cell targeted therapies include Vedolizumab, an a4b7 integrin blocker, which has shown some clinical efficacy in maintenance of remission in CD [30], [31]. As a selective antibody against the a4b7 integrin unit, Vedolizumab largely targets lymphocyte trafficking by binding to a4b7 on T cells, preventing interactions with endothelial cells via MAdCAM-1, which would typically allow homing of lymphocytes into the inflamed tissue [32]. Owing to the specificity of Vedolizumab's binding to a4b7 exclusively, the selective mechanism of action translates to a relatively efficacious and safe option for treatment of moderate to severe CD, although low risks of infection should still be monitored in the maintenance phase [30].

Biologic therapy with anti-TNF agents remain to be the most efficacious therapeutic strategy in a large fraction of patients with moderate to severe CD [33], especially among early responders [34]. Many anti-TNF inhibitors have been developed to deescalate proinflammatory TNF signaling through primarily binding both membrane-bound (and soluble) TNF [32]. Membrane-bound TNF inhibition through monoclonal antibodies induces recruitment and activation of caspase-mediated apoptosis, subsequently inducing death. Besides cell death mechanisms, anti-TNF agents have also clinically shown to downregulate MAdCAM-1, which is not observed in anti-TNF refractory patients [35]; as discussed earlier, this is consistent with mechanisms by which Vedolizumab inhibits lymphocyte trafficking into the inflamed tissue, and thus could be viewed as complementary therapeutic strategies. Despite the various modes of anti-TNF inhibition by current agents, ~40% of patients still show no response to anti-TNF treatment, likely due to delayed treatment institution [36], and incomplete and non-specific cellular targeting [2], [4] (Table 1). In addition to earlier treatment institution, tight control and patient monitoring is instructive for switching to alternative therapeutic strategies. Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23, which inhibits binding of these cytokines to their cognate receptors, thus reducing immune cell activation [37]. It alone showed a clinical response rate of 53% (compared to 30% in the placebo arm) [38], with limited serious adverse effects. In addition, primary or secondary anti-TNF non-responders also show clinical response to Ustekinumab [39], [40], [37] potentially due to the additional targeting of factors produced by innate lymphoid cells (Table 1). Studies have also shown that combination of anti-TNF therapies with immunosuppressives is more efficacious than either agent alone [41].

For further complications faced by treatment-refractory patients, such as severe fistulizing disease, autologous stem cell transplantation has shown to be effective especially in perianal disease [42]; Table 1; ongoing clinical trials [43] will illuminate the effectiveness in this alternative approach, especially for fibrotic complications.

While treatment recommendations for different stages and complications of CD remain complex, understanding mechanisms of action, cellular targets, and monitoring clinical efficacy over time, provides us with a strong foundation upon which to move towards novel personalised combination treatment strategies.

3. Lessons learned from cellular, molecular, and functional genetic studies

3.1. The NOD2 paradox and gut-specificity of myeloid cell replenishment and monocyte differentiation

As opposed to most tissues, tissue-resident macrophages in the intestine are constantly replenished from circulating peripheral blood monocytes, with the local environment influencing cellular interactions and differentiation fate [44]. Constant recruitment of monocytes into the intestinal lamina propria is highly dependent on the CCL2-CCR2 axis [45]; CD14+ monocytes accumulate in the mucosa of IBD patients [2,46], and this is in part due to elevated levels of the monokine CCL2, produced by fibroblasts. Other secreted mediators from the inflamed tissue (such as G-CSF, IL6, Reactive Oxygen Species (ROS) and sustained TLR activation) prime HSCs in the bone marrow to preferentially differentiate along the Myeloid Derived Progenitor lineage (Fig. 1). This program, termed myelopoiesis, enhances proliferation of monocyte populations, which egress from the bone marrow, enter the peripheral blood, and are ultimately recruited to the inflamed tissue.

A key driver of chronicity in CD is the sustained exposure to bacteria; since NOD2 serves to recognise and respond to pattern associated molecular patterns (PAMPs) presented by bacterial moieties, it is perhaps surprising that functional loss of NOD2 increases disease risk. Recent work has helped to answer key elements of this long-standing paradox; pathogenicity of NOD2-driven fibrostenotic CD is in part due to activation of a pathogenic cellular myeloid-stromal niche [47]. CD14+ monocytes from NOD2-mutation carriers differentiate into inflammatory macrophages and activated collagen^{hi}-expressing cells upon being exposed to secreted factors in the inflamed lamina

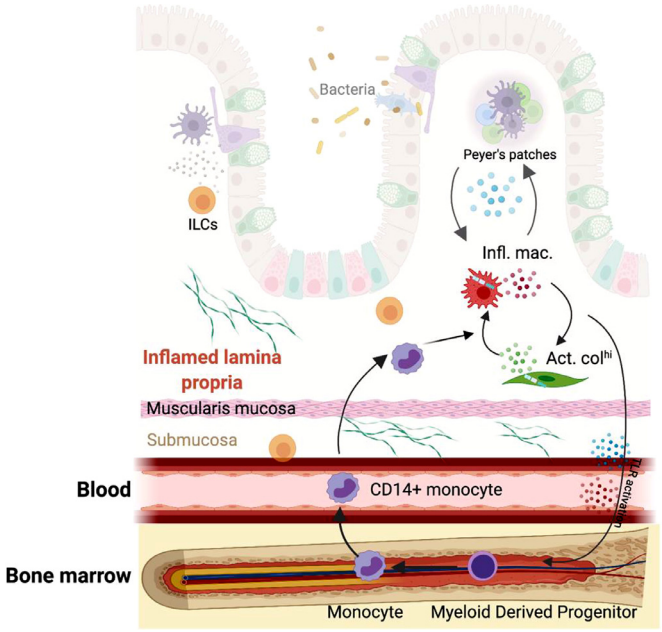


Fig. 1. Infiltrating monocytes sustain plasticity in the inflamed gut, Hematopoietic Stem Cells (HSC) exit quiescence and undergo differentiation, preferentially along the Myeloid Derived Progenitor lineage in inflammatory diseases. Proliferating monocytes egress from the bone marrow and enter the peripheral blood. Infiltrating monocytes are recruited to the inflamed lamina propria by secreted monokines (CCL2) and are exposed to an activated inflammatory and fibrotic state in the diseased tissue. CD14+ monocytes differentiate into inflammatory macrophages (Infl. macs) and activated fibroblast-like collagen-high expressing cells (Act. col^{hi}). These cells communicate with Peyer's patches of the small intestine, Dendritic Cells, ILCs, T cells, B Cells, and epithelial cells, to respond to chronic bacterial exposure. The activated myeloid-stromal niche secretes factors to prime HSCs to continue differentiating along the myeloid lineage to propagate this cycle.

propria (Fig. 1). Through sustained production of chemokines and cytokines (in particular, those belonging to the gp130 family), along with their spatial proximity, activated macrophages and collagen^{hi}-expressing cells form a pathogenic niche. This cell circuit also communicates with secondary lymphoid structures in the small intestine (Peyer's patches) [48], other immune cells (Dendritic Cells, ILCs, T cells, B Cells) [2], and epithelial cells, sustaining pathogenic activation.

3.2. Perturbation of cell circuits and chronicity of disease complexity

How heterotypic cell crosstalk maintains both homeostasis and disease pathogenesis over time is an active area of ongoing research. The reciprocal relationship between macrophages and fibroblasts has been increasingly underscored in both tissue homeostasis and disease [2], [4], [49], [50], beyond their independent roles in contributing to disease pathogenesis [44], [45], [51], [52]. Mathematical modeling of stable cell systems has allowed us to infer consequences of internal and external perturbations more precisely; design principles of stable macrophage-fibroblast systems involve growth factors (specifically CSF1 and PDGFA) that are necessary and sufficient for macrophage-fibroblast homeostasis *in vitro* [49]. Importantly, this study showed that cell-cell contact was critical for the of the macrophage-fibroblast circuit stability, which could point to necessary cellular programs that maintain homeostasis, and disruptions in circuits that result in disease.

As the macrophage-fibroblast cellular crosstalk has proven to be key in the pathogenesis of CD [2], [47], a logical next line of further investigation is understanding how their relationship is sustained systemically throughout disease progression. A key factor driving sustained infiltration of CD14+ monocytes in CD (in addition to chemokine-dependent recruitment), could be the cumulative effect of years of bone marrow priming, especially patients carrying loss-of-function NOD2 mutations (Fig. 1). Long term TLR activation, sustained production of cytokines, and ROS production during inflammation, can enhance differentiation and proliferation of myeloid-derived cells from the bone marrow [53]. At the level of *in vivo* intestinal challenge, dextran sodium sulphate treatment in mice models of colitis increases the monocytic compartment of the bone marrow [54], and recently proposed hypotheses regarding macrophage imprinting [55] also suggest that plasticity is more restricted to the infiltrating, and not residential populations. This is exemplified by the ability of infiltrating CD14+ monocytes to differentiate towards activated fibrotic cell states upon contact with fibrotic milieu [52], [56], especially in the case of NOD2 loss [47] (Fig. 2a). It remains to be determined at what level targeting this multi-step disease process can most effectively occur.

Tight transcriptional control of multipotent cells is likely at play here. WT1 and STAT3[47] are two such transcription factors controlling transient and sustained activation of the myeloid-stromal niche, which ensures maintenance of chronicity and cell plasticity (Fig. 2b). Specifically, WT1 is a transcription factor that has been implicated in myofibroblast transformation in fibrotic lung disease [57] and in mesothelial and fibroblastic stromal cells in homeostasis and disease [58], [59] *WT1* is enriched in the CD14+PDGFRA+ subset of activated fibroblasts, enhanced in NOD2-deficient *in vitro* and *in vivo* systems, and serves as an upstream transcriptional regulator of genes enriched in activated macrophages and fibroblasts from NOD2 risk allele carriers [47]. In addition, polymorphisms in IL6ST (gp130) and STAT3 (downstream of gp130 signaling) have been reported in CD patients [5], and reduction in pSTAT3 expression has been correlated with therapeutic remission via soluble gp130 inhibition [60].

Taken together, this elucidates a three-hit model of pathogenic niche regulation, in this instance, of NOD-driven CD: 1. genetic perturbations (NOD2 loss), 2. continued priming and cell plasticity (bone marrow egress and CD14+ monocyte infiltration into the ileum), and 3. tight, early (WT1) and sustained (STAT3) control, which provides a new framework upon which disease targeting at the niche level may be attempted (Fig. 2b). Identifying other such pathogenic niches, that are primed by genetic perturbations and aberrant cellular crosstalk, will enable strategies by which we can tailor treatments based on personalised genetic and immune predispositions.

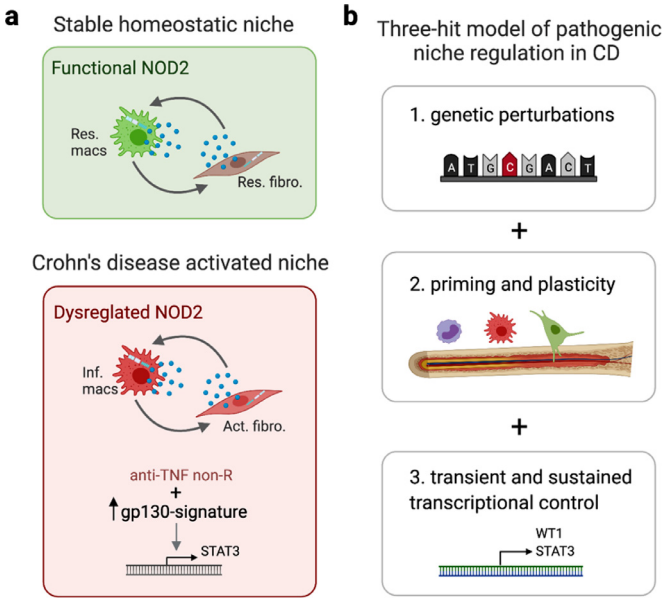


Fig. 2. NOD2 mutations drive a pathogenic myeloid-stromal niche controlled by tight transcriptional control, a. patients who are wildtype for NOD2 are able to maintain appropriate activation and resolution of niche activation. In loss-of-function NOD2 carriers, inf. macs. and act. fibros are inappropriately activated, forming an activated myeloid-stromal niche. Transcriptional signatures (including genes in the gp130 family) upregulated by these cells in NOD2 mutation carriers are highly expressed in anti-TNF non-responders. b. The three-hit model of pathogenic niche regulation starts with underlying genetic mutation carriage, such as those found in NOD2. Over time, priming of the HSC compartment in the bone marrow propagates differentiation and proliferation of CD14+ monocytes, which retain plasticity after infiltrating into the inflamed tissue. Concomitantly, upstream transcriptional regulation of the niche (WT1 early, transient; STAT3 later, sustained) ensures tight control and sustained activation over time.

4. From single-target to combinatorial treatment strategies

4.1. Towards molecular specificity and efficacy with combinatorial treatment strategies

First-line biologics, such as anti-TNF therapy, administered to CD patients only result in ~30% of mucosal healing [61], [62] and ~40% of patients show no clinical benefit to anti-TNF treatment, potentially due to delayed treatment institution[1]. Another approved therapeutic strategy in IBD at the cytokine level, is via inhibition of JAK-STAT pathways[63]. However, given the combinatorial complexity at this level of cytokine signaling, molecular specificity is compromised, and many JAK inhibitors have been associated with substantial side effects[64]. Therapeutic approaches targeting IL6 and IL11 have also been reported in CD, however these have not advanced toward approval for clinical use[65],[66]. Consequently, combination molecular therapy has been increasingly identified as the way forward for clinical success in autoimmunity and cancer, much of which could be effectively achieved through drug repurposing[67],[68]; however, given the lower morbidity/mortality of IBD compared to cancer, the therapeutic window is substantially narrower. Continued identification of multiple molecular targets through single-cell, spatial, and protein-based technologies will help drive therapeutic efforts towards precision IBD.

4.2. Identifying the pathogenic niche: advancing personalised therapeutics in Crohn's disease

Until now, personalised therapeutics in Crohn's disease has been difficult to achieve, partly due to the heterogeneity in tissue and blood cell types affected, lack of clarity on clinical, genetic, and molecular measures of success, and inconsistencies in monitoring and predicting disease course[69]. In recent years, however, pivoting towards proactive, tightly monitored clinical outcomes[70] combined with the increased resolution and identification of novel biomarkers that single-cell technologies and serial tissue sampling have elucidated[2–4], have made the goal of personalised CD treatment seem more attainable.

One such recent advance in fibrostenotic Crohn's disease is through the proposed inhibition of the common cytokine receptor subunit, gp130, by simultaneously targeting both arms of the activated myeloid-stromal niche[47],[71]. Competitive inhibition of the gp130 cytokine binding site prevents activation and downstream STAT3-mediated signaling, ameliorating activation of the myeloid-stromal niche, especially in NOD2 carriers. NOD2 mutations alone have not been reported to correlate with responses to anti-TNF treatment[8],[72]. Early anti-TNF institution allows for tighter control of inflammation through monitoring markers of clinical disease[10], and serial sampling of tissue lesions could add to genetic findings to better predict primary and secondary anti-TNF non-response. Additionally, along the NOD2-family axis, RIPK2 inhibition (Table 1; downstream of NOD2) is another active experimental area of therapeutic targeting, largely through dampening excess inflammation [61],[62]. However, given that RIPK2 functions downstream of NOD2 to propagate signaling, RIPK2 inhibition might instead phenocopy NOD2 loss in patients carrying loss-of-function NOD2 mutations; while myeloid activation might be alleviated, the fibroblast arm might remain activated. More generally, RIPK2 inhibition might work to dampen production of pro-inflammatory cytokines from antigen presenting cells[73] in patients who are wildtype for NOD2, in a NOD2-independent manner[74].

Increased mechanistic insights into specific CD pathogenesis driven by other genetic variants will be a crucial first step to implement the "treat-to-target" approach with the target being patient-specific (Fig. 3). To more effectively capture a larger proportion of disease pathogenicity and variability, these insights should be gleaned from both disease susceptibility (e.g. *NOD2, IL23R*) and non-susceptibility variants (e.g. *FOXO3, HLA-DR*)[69]. While single-target therapeutics such as anti-TNF have been highly effective for some CD patients, substantial limitations of single agent therapies with respect to long-term, complete remission remain. Delineating the cellular and molecular circuitry of tissue lesions[2],[4],[47], [58] underscore the importance of combinatorial strategies targeting cellular niches. As such, newer frameworks of therapeutic targeting in Crohn's disease will be most effective when designing clinical trials based on genetics and genomics, along with serial sampling (Fig. 3). In addition, newer single-cell based multi-omics, combined with spatial-based scRNAseq technologies, will enable efficient characterisation of molecularly defined therapeutic success at the RNA and protein level. Iterating between bulk and single-cell approaches will allow for a) rapid identification of patients who might benefit from one therapeutic strategy over another, and b) further resolution and evaluation of specialised cell subsets that are able to be appropriately targeted by niche-targeting strategies. This will help us inform which patients might benefit from targeting different specialised cell niches, moving towards precision therapeutics in IBD.

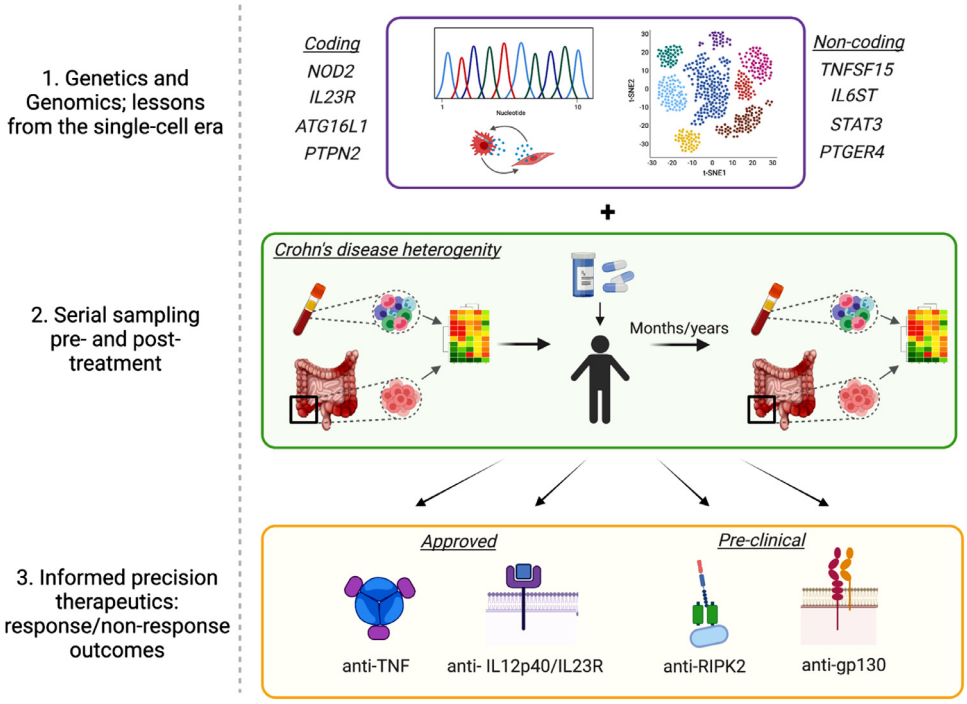


Fig. 3. Crohn's disease heterogeneity: towards tight monitoring and clinical success guided by improved long term outcomes. Genome Wide Association Studies have identified hundreds of risk loci for Inflammatory Bowel Disease. Specific polymorphisms in genes expressed in innate immune cell populations have been described to contribute to the pathogenesis of Crohn's disease. Lessons learned from these genetic association analyses have led to further exploration of specialised cell subtypes using single-cell-omics approaches. Taken together, these provide novel insights into disease pathogenesis at the individual level. Longitudinal transcriptomic studies have been able to profile changes throughout disease trajectory; however, prospective studies focused on pre- and post- treatment changes have been more difficult to accomplish; in particular, dissection of complex molecular programs that define disease heterogeneity. We propose that carefully designed therapeutic clinical trials, informed by genetics, genomics, and serial sampling of tissues from patients will enable informed precision therapeutics based on molecular and histological readouts of response and non-response.

5. Outstanding questions and key considerations

How would we effectively design clinical trials instructed by genetics and genomics to accurately identify the correct therapeutic agent?

With the increasing integration of genomics in clinical practice in the personalised medicine era, key considerations, including polygenic risk carriage and epigenetics, will further instruct the most accurate therapeutic course for individual patients. Clinical trials guided by this approach could help mitigate primary and secondary therapeutic non-response currently observed in many patients.

How can we identify signatures of therapeutic non-response in bio-naïve patients?

As evaluated in this review, current standard of care approaches are often recommended based on disease duration and severity. However, in order to initiate the most efficacious treatment early in disease, single-cell analyses, GWAS, and machine-learning based approaches could stratify patients molecularly into potential responders vs. non-responders based on their baseline transcriptomic profile prior to treatment initiation.

What molecular responses of treatment success/failure would be used to switch strategies to alternative therapeutics?

Current definitions of therapeutic response often include mucosal healing with histologic remission. Newer advances in single-cell technologies can enhance these measures with the inclusion of cell-type-specific transcriptomic signatures that are representative of larger pathogenic disease modules.

What further safety and efficacy considerations would need to be considered when moving towards combination therapy in CD?

One of the remaining concerns as the IBD field increasingly moves towards combination therapy is the risk of adverse side effects. It will be important to ascertain dosage, optimal duration of treatment, and at what stage of disease treatment approaches will be the most efficacious.

6. Conclusions

Therapeutic non-response and incomplete mucosal healing remain at the center of clinical difficulties when treating patients with moderate to severe Crohn's disease. Despite the primacy of TNF in Crohn's disease pathogenesis[75] and clinical efficacy, combination therapies targeting distinct pathways will likely be required to substantially improve outcomes. In recent years, we have gained substantial insights into molecular signatures and cellular niches that are disrupted during chronic disease progression in IBD[2],[4],[47], revealing novel therapeutic targets.

In Crohn's disease, an important molecular mechanism of disease pathogenesis is likely controlled by continued replenishment of monocytes from the bone marrow, where cells retain plasticity upon entering the inflamed tissue, and are programmed to form pathogenic cellular niches, maintained by tight transcriptional control. Reconciling these molecular findings (among other aberrant cellular circuits[3],[58]) with lessons learned from GWAS, will allow us to move towards combinatorial, precision-based treatment strategies [76] in IBD. This will enable precise tailoring of treatment based on genetics, genomics and molecular signatures, while keeping alternative avenues open to safely adjust to complementary strategies, to achieve clinical success and improved long-term outcomes.

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed and Google Scholar, and references from relevant articles using the search terms "Crohn's disease therapy", "ECCO", "IBD remission", "mononuclear phagocytes", "stromal cells", "bone marrow", "Crohn's disease genetics", "anti-TNF non-response", "gp130 inhibition". Only articles published in English between 1984 and 2021 were included.

Contributors

S.N. and J.H.C. conceptualized the manuscript and content. S.N. performed all literature searches, generated all figures, original tables, and text, and compiled the manuscript. J.H.C. contributed to extensive reviewing and editing. All authors have read and approved of the final version of the manuscript.

Declaration of Competing Interest

S.N. and J.H.C. have filed a provisional patent application with Mount Sinai Innovation Partners (US patent application no. 63/130,035) on repurposing Bazedoxifene for clinical use in a subset of patients with Crohn's disease.

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