Identification of Novel Therapeutic Molecular Targets in Inflammatory Bowel Disease by Using Genetic Databases

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Purpose: Utilization of genetic databases to identify genes involved in ulcerative colitis (UC), Crohn’s disease (CD), and their extra-intestinal manifestations.

Methods: Protein coding genes involved in ulcerative colitis (3783 genes), Crohn’s disease (3980 genes), uveitis (1043 genes), arthritis (5583 genes), primary sclerosing cholangitis (PSC) (1313 genes), and pyoderma gangrenosum (119 genes) were categorized using four genetic databases. These include Genecards: The Human Gene Database (www.genecards.org), DisGeNET (https://www.disgenet.org/), The Comparative Toxicogenomics Database (http://ctdbase.org/) and the Universal Protein Resource (https://www.uniprot.org/). NDex, Network Data Exchange (http://www.ndexbio.org/), was then utilized for mapping a unique signal pathway from the identified shared genes involved in the above disease processes.

Results: We have detected a unique array of 20 genes with the highest probability of overlay in UC, CD, uveitis, arthritis, pyoderma gangrenosum, and PSC. Figure 1 represents the interactome of these 20 protein coding genes. Of note, unique immune modulators in different disease processes are also noted. Interleukin-25 (IL-25) and monensin-resistant homolog 2 (MON-2) are only noted in UC, CD, pyoderma gangrenosum, and arthritis. Arachidonate 5-lipoxygenase (ALOX5) is involved in UC, CD, and arthritis. SLCO1B3 is exclusively involved with pyoderma gangrenosum, UC, and CD. As expected, TNF involvement is noted in CD, UC, PSC, and arthritis. Table 1 depicts the detailed result.

Conclusion: Our work has identified a distinctive set of genes involved in IBD and its associated extra-intestinal disease processes. These genes play crucial roles in mechanisms of immune response, inflammation, and apoptosis and further our understanding of this complex disease process. We postulate that these genes play a critical role at intersecting pathways involved in inflammatory bowel disease, and these novel molecules, their upstream and downstream effectors, are potential targets for future therapeutic agents.

Keywords: inflammatory bowel diseases, IBD, ulcerative colitis, UC, Crohn’s disease, CD, arthritis, primary sclerosing cholangitis, PSC, uveitis, pyoderma gangrenosum

Plain Language Summary

In the era of translational and personalized medicine, Inflammatory Bowel Disease (IBD) remains a complex disease. This complicated disease presents with a wide array of symptoms that arise from underlying pathophysiological alterations in the patient’s mucosal immune system, the intestinal microbiome, the patient’s genome, and environmental factors. While the predominant disease manifests with gastrointestinal symptoms, involvement of other organs, including but not limited to the skin, eyes, and bones that present as arthritis, uveitis, and pyoderma gangrenosum, is not uncommon. Though the last decade has identified...
possible genetic factors that confer susceptibility to IBD, the signaling pathways involved in these extra-intestinal manifestations still remain poorly understood. In this study, we use genetic databases to identify an exclusive set of genes that are involved in the extra-intestinal manifestations of IBD and propose these molecules as potential drug targets.

Introduction

Inflammatory Bowel Diseases, which primarily include Ulcerative Colitis and Crohn’s disease, are now increasingly recognized as a complex, multi-factorial constellation of diseases whose incidence has been increasing globally.\(^1,^2\) While the disease is predominantly described as a gastrointestinal disease, symptoms involving other organ systems are increasingly recognized.\(^3,^4\) In the past decade, studies conducted in both animals and human models have suggested that several genetic factors are involved in the pathogenesis of IBD.\(^5-^10\) Animal studies have argued for an immune mediated role for IBD. These studies have utilized techniques like gene deletion, gene mutation, chemical induction, and genetic engineering, where manipulation of several genes, specifically distinct immune regulators increase the genetic susceptibility for IBD; possibly by alteration of host defense mechanisms and modulation of the individual’s microbiome.\(^6,^7,^10\) The human studies on the other hand posit that there is a multi-factorial basis, where genetic alterations in combination with environmental factors have been implicated. This data is derived from studies of inheritance patterns of Crohn’s in monozygotic twins, where a higher incidence of Crohn’s has been noted.\(^7,^8,^11\) Further, association studies of genomewide databases have postulated that more than 230 IBD loci are implicated in the pathogenesis of IBD.\(^12-^14\) However, understanding of the mechanistic basis of extra-intestinal manifestations of IBD still remains limited. Few of the signaling pathways known have been proposed to be shared with host response to various bacteria and other immune mediated disorders which comprise extra-intestinal manifestations. This study aims to identify genes involved in IBD and its’ extra-intestinal manifestations, ie, PSC, pyoderma gangrenosum, arthritis, and uveitis. We hypothesize a network of signaling cascades exist that form the etiological backbone of these diseases, their diverse manifestations, and can offer potential pharmaceutical targets.

Results

Our initial analysis from the GeneCards: The Human Gene Database, DisGeNET, The Comparative Toxicogenomics Database and the Universal Protein Resource, identified 3783 genes in UC, 3980 genes in CD, 1043 genes in uveitis, 5583 genes in arthritis, 1313 genes in PSC, and 119 genes in pyoderma gangrenosum. Of note, genes identified from these databases do not directly implicate casualty, but are a summation of altered genes in the respective disease state, from studies of animal models, tissue culture, and human databases. We then identified a unique array of 20 genes, that had the highest probability of involvement in UC, CD, uveitis, arthritis, pyoderma gangrenosum, and PSC. A signaling network or interactome (Figure 1) was then formulated using the NDex, Network Data Exchange.\(^15,^16\) Of note, this genetic array had a strong emphasis on immune modulators, further arguing for an immune basis in the extra-intestinal presentations of IBD (Table 1 and Figure 1). As expected, we noted Tumor necrosis factor (TNF) involvement in CD, UC, PSC, and arthritis. Further, C-C motif chemokine ligand 2 (CCL2), a chemokine essential for recruitment of monocytes, memory T-cells, and dendritic cells, and an important agent in Protein kinase B (AKT) signaling and Pigment epithelium derived factor (PEDF) pathways, was also involved in CD, UC, arthritis and uveitis.\(^17\) Interestingly, unique modulators were also identified as common nodes in distinctive disease processes. We noted that two immune modulators (a) Interleukin-17A (IL-17A), a proinflammatory cytokine, and (b) Interleukin-21 (IL-21), a regulator of Natural Killer (NK) cells and cytotoxic T cells, are both implicated in CD, UC, uveitis, PSC, and arthritis.\(^18,^19\) Arachidonate 5-lipoxygenase (ALOX5), an important member of the lipoxygenase gene family, was exclusively involved in UC, CD, and arthritis.\(^20\) Fas
Figure 1 Signaling map of genes (interactome) overlapping in inflammatory bowel disease (UC and CD) and its extra-intestinal manifestations.

Ligand (FASLG), an important player in apoptosis and death receptor, and CCR5, a known HIV receptor, were detected in UC, CD, PSC, uveitis, and arthritis, but not in pyoderma gangrenosum.\textsuperscript{21,22} MON2, a regulator of endosome to golgi trafficking and IL-25, a mediator in IL-17 and PEDF signaling, were only noted in CD, UC, pyoderma gangrenosum, and arthritis.\textsuperscript{23,24} In contrast, SLCO1B3, which encodes for organic anion transporter, was exclusively involved in Pyoderma gangrenosum, UC and CD.\textsuperscript{25} (Table 1)

Discussion

IBD is a complex group of heterogeneous disorders, with an underlying multifactorial pathophysiological basis. A dysregulation between environmental, underlying human microbiome, and genetic susceptibility factors, is hypothesized to play a crucial role in varying manifestation of IBD.\textsuperscript{1,2,5–13} In our study, we have used genetic data sets to look for overlapping genes involved in IBD and its’ extra-intestinal disease forms (like arthritis, uveitis, and pyoderma gangrenosum). Our study supports the theory that immune modulators are critical mediators in extra-intestinal manifestations of IBD. These genes allude towards cross-sectional nodes, that could further implicate to involvement of different signal transduction molecule cascades in different manifestations of IBD.

We hypothesize that these overlapping molecules act as focal points of intersecting signal transduction pathways and are involved in distinctive clinical presentations of IBD and hence are potential therapeutic targets. While our in silico analysis is limited by a lack of wet-lab experiments, it highlights interesting candidate molecules and possible network pathways, which can be utilized in future more focused experimental designs. We believe our analysis consolidates existing information and lays the groundwork for future in vitro and in vivo studies, dedicated towards understanding the pathophysiology of this complex disease. In vitro tissue culture experiments looking at overexpression, underexpression, and protein–protein interactions are key in elucidating the specific function of these molecules; which in turn would offer more insights towards in vivo studies, either in animal models or towards clinical trials in patients with IBD.

Of particular interest in this regard, and noteworthy here is IL-17A, which was identified as a potential target in our analysis.\textsuperscript{29,30} Secukinumab, an anti-IL-17A monoclonal antibody, was found to be safe and efficacious in psoriasis and rheumatoid arthritis.\textsuperscript{29,30} However, higher adverse events were noted in patients with moderate-to-severe CD.\textsuperscript{30} This highlights an inherent limitation of in silico database analyses and in vitro studies, where there is an inability to re-create the unique human intestinal immunological environment and the complex interactions of the host immune system with the gut microbes, which is perhaps critical in the pathophysiology of IBD. This could, in turn, be a limitation in direct translation of data retrieved from in silico analyses to animal model studies and then in therapeutic clinical trials.

Lastly, databases are ever changing, and comprise information from both animal and human tissues. Thus, we anticipate advancement in cell–cell networking, genomewide association studies to keep evolving over time. Though these ever-growing database repositories do offer the advantage of high throughput screening, we acknowledge that this information still has to be used in conjunction with wet lab data to advance our understanding of IBD.\textsuperscript{31–33}

Conclusion

Our work identifies a unique set of 20 genes involved in IBD and associated extra-intestinal diseases. These
Table 1 Genes Overlapping in IBD (UC and CD) and Its Extra-Intestinal Manifestations (Uveitis, Arthritis, Primary Sclerosing Cholangitis and Skin Manifestations – Pyoderma Gangrenosum); with the Individual Gene, Specific Disease Processes, and Gene Function Listed

| SN # | Genes | Conditions | Pathways* |
|------|-------|------------|-----------|
| 1    | IL17A | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Mucin expression in CF via IL6, IL17, IL27 mediated pathway, PDGF signaling, Th17 differentiation, RA pathway |
| 2    | NOD2  | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Activated TLR4 signaling, NF-kappaB Pathway, NOD Pathway, Deubiquitination |
| 3    | TNF   | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | TNFRI pathway, IL6 pathway, STAT 3 pathway, Death Receptor signaling, Toll Like Receptor signaling |
| 4    | CCR6  | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Akt Signaling, Defensins, GPCR Signaling |
| 5    | CXCL8 | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | PEDF induced signaling, Toll-like receptor signaling pathway, TGF-Beta Pathway, GPCR ligand binding |
| 6    | IL1B  | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | PEDF induced signaling, Toll-like receptor signaling pathway, TGF-Beta Pathway, GPCR ligand binding, ERK Signaling |
| 7    | NLRP3 | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | NLR signaling pathway, Innate immune system, metabolism of proteins, Toll-like receptor signaling pathway |
| 8    | MPO   | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Innate immune system, Folate Metabolism, NF-kappaB Pathway, Cytochrome P450 |
| 9    | IL1RN | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | NF-kappaB Pathway, IL1 Signaling, PEDF induced signaling, Toll-like receptor signaling pathway |
| 10   | ITGB2 | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | MAPK Erk Pathway, PPAR Pathway, Rho Family GTPases, FAK1 signaling, Actin nucleation, and Branching |
| 11   | FPRN22| UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | PAK pathway, CTLA4 signaling, NF-kappaB Pathway |
| 12   | MMP9  | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Matrix Metalloproteinase's, Integrin pathway, Degradation of extracellular matrix, Innate immune system |
| 13   | ICAM1 | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | VCAM-1/CD106 signaling, Folate metabolism, Interferon gamma signaling |
| 14   | GPBAR1| UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | GPCR signaling |
| 15   | ITGA4 | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | GPCR signaling, PPAR pathway, FAK1 signaling, Focal adhesion, Actin Nucleation, and branching |
| 16   | F3    | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Formation of fibrin clot, AGE-RAGE signaling pathway, complement, and coagulation cascades |
| 17   | SELE  | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | AGE-RAGE signaling pathway, Cell adhesion molecules, VEGF Signaling |
| 18   | SPP1  | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | FAK1 signaling, ERK signaling, Toll-like receptor signaling pathway, ECM receptor interaction, Focal adhesion |
| 19   | IL1R1 | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | PEDF Signaling, Toll-like receptor signaling pathway, TGF-Beta Pathway |
| 20   | ELANE | UC, CD, Arthritis, Uveitis, PSC, and Pyoderma Gangrenosum | Degradation of extracellular matrix, Innate immune system, Transcriptional misregulation in cancer |
| 21   | IL20  | UC, CD, Arthritis, Uveitis, and PSC | PEDF, TGF beta, AKT signaling, Rho family GtPase, PAK pathway |
| 22   | IL21  | UC, CD, Arthritis, Uveitis, and PSC | PEDF, Rho GtPase, PAK, AKT, Th17 |
| 23   | IL2RA | UC, CD, Arthritis, Uveitis, and PSC | Apoptosis, IL-receptor SHC signaling, PEDF pathway, TGF Beta, AKT |
| 24   | SAG   | UC, CD, Arthritis, Uveitis, and PSC | Rhodopsin mediated signal pathway |
| 25   | IFNG  | UC, CD, Arthritis, Uveitis, and PSC | Allograft rejection, Immune response INF γ signaling pathway, Toll Pathway |
| 26   | CXCR3 | UC, CD, Arthritis, Uveitis, and PSC | Class A/1, GPCR, Neuropeptide signaling, AKT |
| 27   | CXCL10| UC, CD, Arthritis, Uveitis, and PSC | PEDF, Class A/1 receptor, Rho family GtPase, Toll like receptor |
| 28   | CTLA4 | UC, CD, Arthritis, Uveitis, and PSC | PKC-theta, CD28, Cell adhesion molecules |

(Continued)
Table 1 (Continued).

| SN # | Genes     | Conditions                      | Pathways*                                                                 |
|------|-----------|---------------------------------|----------------------------------------------------------------------------|
| 29   | CCL2      | UC, CD, Arthritis, Uveitis, and PSC | PEDF, TGF beta, AKT, and Rho                                               |
| 30   | LTA       | UC, CD, Arthritis, Uveitis, and PSC | PEDF, Rho, TRAF, NF-Kb                                                     |
| 31   | IL10      | UC, CD, Arthritis, Uveitis, and PSC | PEDF, TGF, Rho, AKT                                                       |
| 32   | CCR5      | UC, CD, Arthritis, Uveitis, and PSC | HIV Receptor-Class A1, A2, GPCR, Neuropeptide, and Chemokine               |
| 33   | RBP3      | UC, CD, Arthritis, Uveitis, and PSC | Visual cycle, metabolism of fat-soluble vitamins, GPCR signaling           |
| 34   | CXCR1     | UC, CD, Arthritis, Uveitis, and PSC | IL8-R pathway-Class A1, GPCR, Neuropeptide signaling, Cell Adhesion ECM    |
|      |           |                                 | modeling, Inhibitory actions of lipoxins on SOD                           |
| 35   | FASLG     | UC, CD, Arthritis, Uveitis, and PSC | Apoptosis and Death receptor                                               |
| 36   | TNFRSF1A  | UC, CD, Arthritis, Uveitis, and PSC | TWEAK, Apoptosis, TGF, PEDF                                                 |
| 37   | TLR4      | UC, CD, Arthritis, Uveitis, and PSC | TRAF, Toll like receptor pathway                                            |
| 38   | IL28B     | UC, CD, Arthritis, Uveitis, and PSC | PEDF, AKT, TGF-beta, IL-22 pathway                                         |
| 39   | NLRCD4    | UC, CD, Arthritis, and Uveitis  | Gene Expression, innate immune system, Legionellosis, and NLR signaling  |
| 40   | SLC22A4   | UC, CD, Arthritis, and PSC      | Phospholipase D signaling pathway, Transport of metal ions, glucose, bile salt, and organic acids |
| 41   | AREG      | UC, CD, Arthritis, and PSC      | TGF Beta, Rho Gpases, Nanpg on mammalian ESC pluriopotency                |
| 42   | IL25      | UC, CD, Arthritis, and PSC      | IL17 signaling pathway, PEDF induced signaling, TH2 differentiation       |
| 43   | MON2      | UC, CD, Arthritis, and Pyoderma  | Regulates endosome to golgi trafficking                                    |
| 44   | FASN      | UC, CD, and Arthritis           | AMPK signaling pathway, Fatty acid biosynthesis, Fatty acid metabolism, Insulin signaling pathway, Metabolic pathways |
| 45   | LZTR1     | UC, CD, and Arthritis           | Protein modification and ubiquitination                                    |
| 46   | LAMP2     | UC, CD, Arthritis               | Autophagy, Platelet, and Neutrophil degranulation                         |
| 47   | ALOX5     | UC, CD, and Arthritis           | arachidonic acid, LT, Selenium pathway                                     |
| 48   | SLCO1B3   | UC, CD, and Pyoderma Gangrenosum | Bile acid, bile salt metabolism                                            |

Notes: *Source – Kegg pathway database (https://www.genome.jp/kegg/pathway.html); UniProt (https://www.uniprot.org) and Genecards – the human genome database (https://www.genecards.org)."26–28

Abbreviations: UC, ulcerative colitis; CD, Crohn’s disease; PSC, primary sclerosing cholangitis; IL-17A, interleukin 17A; NOD2, nucleotide binding oligomerization domain containing 2; TNF, tumor necrosis factor; CCR6, C-C motif chemokine receptor 6; CXCL8, C-X-C motif chemokine ligand 8; IL1B, interleukin 1 beta; NLRP3, NLR family pyrin domain containing 3; MPO, myeloperoxidase; IL1RN, interleukin 1 receptor antagonist; ITGB2, integrin subunit beta 2; PTEN22, protein tyrosine phosphatase non-receptor type 22; MMP9, matrix metalloproteinase 9; ICAM1, intercellular adhesion molecule 1; GPRAR1, G protein-coupled bile acid receptor 1; ITGAM, integrin subunit alpha 4; F3, coagulation factor III, tissue factor; SELE, selectin E; SPP1, secreted phosphoprotein 1; IL-1R1, interleukin 1 receptor type 1; ELANE, elastase, neutrophil expressed; IL-20, interleukin 20; IL-21, interleukin 21; IL-2RA, interleukin 2 receptor subunit alpha; SAG, S-antigen vascular anti-FGF, interferon gamma; CXCR3, C-X-C motif chemokine receptor 3; CXCL10, C-X-C motif chemokine ligand 10; CTLA4, cytotoxic T lymphocyte associated protein 4; CCL2, C-C motif chemokine ligand 2; LT A, lymphotixin alpha; IL10, interleukin 10; CCR5, C-C motif chemokine receptor 5; RBP3, retinoic acid binding protein 3; CXCR1, C-X-C motif chemokine receptor 1; FASLG, Fas ligand; TNFRSF1A, TNF receptor superfamily member 1A; TLR4, toll like receptor 4; IL2RB, interleukin 2 receptor subunit beta; NLRC4, NLR family CARD domain containing 4; SLC22A4, solute carrier family 22 member 4; AREG, amphiregulin; IL25, interleukin 25; MON2, MON2 homolog, regulator of endosome-to-golgi trafficking; FASN, fatty acid synthase; LZTR1, leucine zipper like transcription regulator 1; LAM22, lysosomal associated membrane protein 2; ALOX5, arachidonate 5-lipoxygenase; SLCO1B3, solute carrier organic anion transporter family member 1B3; CF, cystic fibrosis; IL-6, interleukin 6; IL-17, interleukin 17; IL-27, interleukin 27; P450, platelet derived growth factor; RA pathway, retinoic acid pathway; NF-kappaB, nuclear factor kappa light chain enhancer of activated B cells; NOD, nucleotide binding oligomerization domain; STAT 3, signal transducer and activator of transcription 3; AKT, protein kinase B; GPCR, G protein coupled receptor; PPAR, peroxisome proliferator-activated receptors; FK1, focal adhesion kinase 1; PAK, p21 activated protein kinase; VAM1, vascular cell adhesion molecule 1; AGE, advanced glycation end products; RAGE, receptor for advanced glycation end products; Rho family, Ras homolog family; Class A11, rhodopsin like receptors; PKC, protein kinase C; HIK, human immunodeficiency virus; IL-8, interleukin 8; ECM, extracellular matrix; SOD, superoxide dismutase; TWEAK, TNF related weak inducer of apoptosis; TRAF, tumor necrosis factor receptor associated factor; ESC, embryonic stem cells; AMPK, AMP-activated protein kinase; LT, leukaotriene.

Genes are involved in various aspects of cellular processes and signal transduction like processes of apoptosis, inflammation, and immune response. We propose that bioinformatics and system immunology is a potent tool to dissect the complex signaling networks in IBD, and further exploration of upstream and downstream effectors of these candidate genes may help in greater understanding of IBD and its extra-intestinal manifestations.

Disclosure
The authors declare that they have no personal nor financial or non-financial interests for this work.
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