


Mucosal IgG in inflammatory bowel disease – a question of (sub)class?

Tomas Castro-Dopico ^a and Menna R. Clatworthy^{a,b,c}

^aMolecular Immunity Unit, Department of Medicine, University of Cambridge, Cambridge, UK; ^bNIHR Cambridge Biomedical Research Centre, Cambridge, UK; ^cCellular Genetics, Wellcome Trust Sanger Institute, Hinxton, UK

ABSTRACT

Immunoglobulins (Igs) form a cornerstone of mucosal immunity. In the gastrointestinal tract, secretory IgA and IgM bind to commensal microorganisms within the intestinal lumen to prevent them from breaching the intestinal epithelium – a process known as immune exclusion. In recent years, there has been renewed interest in the role of IgG in intestinal immunity, driven in part by a genetic association of an affinity-lowering variant of an IgG receptor, FcγRIIA, with protection from ulcerative colitis (UC), a subclass of inflammatory bowel disease (IBD). We recently demonstrated a role for IgG and Fcγ receptor signalling in driving pathogenic IL-1β production by colonic mononuclear phagocytes and the subsequent induction of a local type 17 response in UC. Here, we discuss the potential relevance of our observations to the other major subclass of IBD – Crohn's disease (CD) – where the genetic association with *FCGR* variants is less robust and consider how this may impact therapeutic interventions in these disease subsets.

ARTICLE HISTORY

Received 10 June 2019
Accepted 31 July 2019

KEYWORDS

IgG; Fcγ receptors; inflammatory bowel disease; ulcerative colitis; Crohn's disease; subclasses

Introduction

Secretory immunoglobulin (IgA) and IgM antibodies play a fundamental role in maintaining mutualism between the host and the microorganisms that colonise our mucosal surfaces.¹ At these sites, IgA limits microbial penetrance, promotes bacterial elimination, and educates the mucosal immune system through antigen capture.^{2–4} However, IgG has also been described in the healthy human and murine gut.⁵ Maternal IgG plays a key role in neonatal intestinal immunity where it provides mucosal protection and immune education prior to the development of post-natal immunity.^{6–8} However, intestinal IgG responses are limited in the healthy adult gut, given the potential pro-inflammatory effects of this antibody isotype in complement fixation and immune cell activation via Fcγ receptor (FcγR) engagement.

In the context of intestinal infection, several studies have identified a critical role for B cells and IgG in pathogen containment and elimination – dominant effects that supersede the involvement of IgA and IgM.^{9–13} For example, IgG is required for neutralization of *Citrobacter rodentium* in mice, a model of attaching-effacing enteropathogenic *Escherichia coli*

infection in humans. This protection can be passively transferred to offspring *in utero* and through breast milk.^{9,11} Therefore, mucosal immunity retains the capacity to elicit potent IgG-mediated inflammatory responses if required to promote pathogen clearance.

Historical studies have identified an increase in mucosal IgG responses in patients with inflammatory bowel disease (IBD), a chronic relapsing inflammatory disease of the gastrointestinal (GI) tract.^{14,15} Indeed, intestinal IgG⁺ cells and circulating anti-commensal IgG have been observed in both major subclasses of IBD, Crohn's disease (CD) and ulcerative colitis (UC). However, the functional consequences of this response remained largely unknown, given the long-standing belief that B cells do not participate in IBD pathogenesis. Our recent study sheds light on the mechanisms by which mucosal IgG drive intestinal inflammation in UC, through the engagement of FcγRs on local macrophages, leading to subsequent type 17 T cell activation. However, whether this represents a universal pathogenic mechanism across IBD subsets is unclear, particularly considering the differing strength of genetic association between *FCGR* variants and UC and CD susceptibility.

Inflammatory bowel disease

Immunopathology and genetics

IBD is divided into two major subclasses, CD and UC, that differ in their clinicopathological phenotype.¹⁶ CD can involve any part of the intestine from mouth to anus and is characterised by transmural inflammation, whereas UC is confined to the large intestine and inflammation is typically limited to the mucosa. At the core of disease susceptibility is an aberrant immune response towards the microbiota, precipitated by poorly defined environmental and genetic factors. Intestinal epithelial, stromal, and myeloid cells produce key inflammatory mediators, including tumor necrosis factor (TNF) and interleukin (IL)-23, while adaptive immunity is skewed towards

mixed Th1/Th17 and Th2/Th17 responses in CD and UC, respectively. Unsurprisingly, immunosuppressive agents form the mainstay in IBD therapy, with monoclonal antibodies that target some of these cytokines, particularly TNF and IL-23, showing success in the clinic.¹⁷⁻¹⁹

While CD and UC share several genetic associations, including components of the IL-23-Th17 axis, there are also major genetic determinants of disease susceptibility that are unique to each IBD subclass (Figure 1).²⁰ UC susceptibility is linked to genes involved in epithelial barrier function and the major histocompatibility complex region, near HLA class II genes. In contrast, CD is linked to defects in microbial sensing. NOD2 mutation homozygotes exhibit ~20-fold increased risk for CD,²¹ while a further susceptibility locus maps to

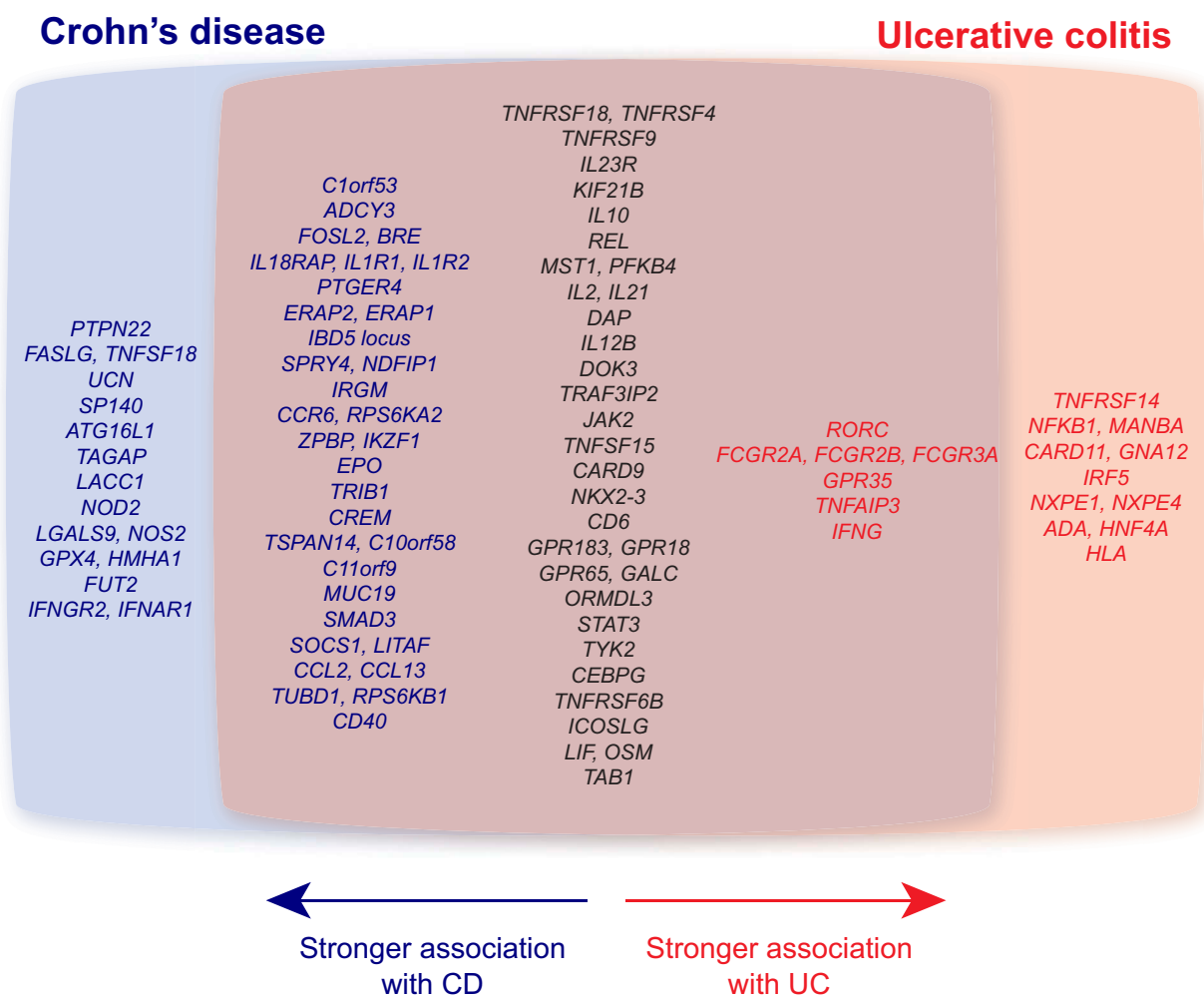


Figure 1. Major genetic associations in inflammatory bowel disease. Venn diagram of major genetic associations in IBD (candidate genes from single nucleotide polymorphisms (SNPs) with P value $< 1 \times 10^{-13}$).²⁰ Common genes are subdivided based on greater association with CD (blue) or UC (red).

the autophagy gene *ATG16L1*, a process required for growth restriction of some intracellular bacteria, such as *Salmonella typhimurium*.²² Indeed, several IBD susceptibility loci map to genes involved in primary immunodeficiencies (PIDs), disorders characterised by severe susceptibility to infection, including *CARD9*, *IFNGR2* and *STAT3*, particularly in CD.²⁰

Fcγ receptors in IBD

The potential involvement of IgG and FcγRs in IBD pathogenesis was highlighted by the consistent identification of an activating Fcγ receptor gene variant, *FCGR2A*-R/H131, among associated risk loci in UC across genome wide association (GWA) studies in multiple populations.^{20,23} Specifically, the *FCGR2A* variant rs1801274 encoding a receptor with low affinity for IgG (R131) is associated with protection from UC,²³ suggesting a pathogenic role for IgG. FcγRs are cell surface receptors widely expressed by innate immune cells and B cells that bind to the Fc domain of IgG antibodies.²⁴ There are several activating FcγRs in both humans (FcγRI, FcγRIIA, FcγRIIA, and FcγRIIB) and mice (FcγRI, FcγRIII, and FcγRIV), whose crosslinking by IgG immune complexes or opsonized cells leads to phosphorylation of immunoreceptor tyrosine based activating motifs (ITAMs) located on the intracellular domain or on the associated common γ-chain, leading to cellular activation.²⁵ There is also a single inhibitory receptor in both humans and mice, FcγRIIB, that contains an intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM) that can recruit phosphatases to signalling synapses to dampen IgG-mediated activation signalling.

In our recent study, we demonstrated a significant enrichment of IgG-opsonized commensals in stool samples from patients with UC that positively correlated with disease severity.²⁶ Transcriptomic analysis of human colonic UC biopsies demonstrated an enrichment of genes associated with activating *FCGR* signalling, and implicated an immune cell network, at the heart of which was IL-1β-producing intestinal FcγRIIA-expressing mononuclear phagocytes (MNPs). Having demonstrated FcγRIIA-dependent IL-1β production by human macrophages in response


to IgG *in vitro*, we validated a functional effect of this IgG-macrophage axis *in vivo* by using a mouse model of intestinal inflammation – dextran sodium sulfate (DSS)-induced colitis. In this setting, manipulation of the intestinal MNP FcγR signal strength, using transgenic mouse strains with varying inhibitory FcγR expression, regulated colitis severity. Exacerbated FcγR signalling increased colonic MNP IL-1β production and subsequent neutrophil infiltration and local type 17 immunity. In contrast, MNP-specific overexpression of FcγRIIB reversed this susceptibility, directly linking the FcγR-MNP axis to disease progression. Furthermore, it is noteworthy that elevated FcγRIIA expression was linked to infliximab-resistant UC, suggesting this network may also contribute significantly to treatment-refractory UC.

Immunoglobulin G in Crohn's disease and ulcerative colitis

Our study focused on the pathogenesis of UC, given its stronger genetic link to FcγRIIA variants (CD *P* value = 1.53×10^{-7} ; UC *P* value = 2.12×10^{-38})²⁰ (Figure 1). Whether similar immune pathways contribute to CD pathogenesis is unclear. It is noteworthy that although potent mucosal IgG responses are also observed in CD, subsequent studies have demonstrated significant heterogeneity both between CD and UC and within IBD subclasses in the IgG response, including differences in IgG frequency, subclass distribution, antigen specificity, and glycosylation state (Figure 2).^{14,27–32} Here we discuss some of these differences and how they may be affected by the genetic context of each IBD subclass.

IgG subclasses

Although there is a strong genetic association of *FCGR2A* variants with UC, the link with CD is weaker, despite the fact that mucosal IgG is increased to a similar extent in CD and correlates with disease severity.^{33–35} Asano *et al.* found no association of the *FCGR2A* SNP with CD, a finding confirmed by some GWA studies,³⁶ however, some candidate gene studies have also implicated rs1801274 as protective in CD,³⁷ as did



IgG characteristics

Crohn's disease	IgG ⁺ plasma cells (% total)	Ulcerative colitis
20-40 % ^{a,b}		40-80 % ^{a,c}
IgG1 ≈ IgG2 > IgG3 ^{a,d}	Subclass	IgG1 >> IgG2 > IgG3 ^{a,d}
Agalactosylated ^{e,f} Desialylated	Glycosylation	Agalactosylated ^{e,f}
Commensals ^g GM-CSF ⁱ	Targets	Commensals ^{g,c} pANCA ^h Colon epithelial cells ⁱ

Figure 2. IgG characteristics in Crohn's disease and ulcerative colitis. Summary of the differences in IgG responses between CD and UC patients, including frequency of plasma cell pool, IgG subclass distribution, glycosylation status, and antigen specificity. pANCA = perinuclear anti-neutrophil cytoplasmic antibodies; GM-CSF = granulocyte macrophage-colony stimulating factor.

a large meta-analysis of GWA studies.²⁰ A small candidate gene study also identified an association between *FCGR3A**A559C (rs396991, encoding a valine for a phenylalanine at amino acid 158 in the extracellular domain of the receptor, (FcyRIIIA-F158V)) and CD,³⁸ but this has not been confirmed in larger GWA studies.

One potential explanation for the differing associations of UC and CD with *FCGR* genotypes may lie in the differences observed in IgG subclass distribution and in the mucosal plasma cell pool between the two IBD subclasses. In UC patient biopsies, up to 80% of mucosal plasma cells express IgG, the majority being IgG1⁺ – an inflammatory IgG subclass capable of potent activating FcyR engagement and complement activation.^{39–42} In contrast, IgG⁺ cells make up a smaller fraction of the total mucosal plasma cell pool in CD, with a greater contribution from IgM.^{33,34,39} Importantly, IgG⁺ plasma cells in CD are equally distributed between IgG1 and IgG2 subclasses. IgG2 is known to have reduced inflammatory capacity relative to IgG1, making up a large proportion of the mucosal IgG pool in health.³² Smaller populations of IgG3⁺ cells have been observed in both IBD subclasses, the IgG subclass with most potent complement-fixing and FcyR

signalling capacity.⁴² Furthermore, these studies highlight large inter-individual variability in the magnitude of mucosal IgG that strongly correlates with disease severity, a finding corroborated by ourselves in UC by measuring luminal commensal-bound IgG levels.²⁶ Therefore, IgG appears to associate with both subclasses of IBD, but the level and inflammatory subclass frequency is highest in UC.

Glycosylation

IgG heavy chains are post-translationally modified by glycosylation at asparagine 297 within the Fc region – a modification critically required for effector function – with over 900 glycoforms possible.^{40,43} Unsurprisingly, specific glycoforms can variably and profoundly alter IgG effector function; for example, de-fucosylation increases the binding affinity of IgG for activating FcyRIIIA (but not FcyRIIB) 10–50 fold.⁴⁴ Abnormalities in the IgG glycome have been observed in several autoimmune and inflammatory diseases, including IBD, and following infection.⁴⁵

Severity-dependent agalactosylated IgG, associated with enhanced complement activation, has also been observed in IBD patients, is highest in CD and predictive of poor prognosis in UC.^{46–48} CD patients further exhibit a reduction in IgG sialylation, a modification that promotes anti-inflammatory IgG activity via reduced activating FcyR binding. The specific functional effects of these different IgG glycoforms in IBD patients, however, is unknown. Indeed, a systematic analysis of IgG subclasses and glycosylation state in CD and UC, with parallel information on site-specific disease, disease severity, and treatment response, remains to be performed.

Antigen specificity

As well as differences in the pro-inflammatory potential of IgG between CD and UC patients, differences in antibody specificity between IBD subclasses have also been highlighted. Generally, bone fide commensal reactivity appears to be more widespread in CD.²⁸ Mucosal IgG exhibits greater reactivity towards non-pathogenic commensal

strains and microbial antigens, including flagellin and *Saccharomyces cerevisiae* mannan (ASCA), with little cross-reactivity with non-intestinal bacterial or viral species.^{27,30,49–51} In contrast, the development of autoantibodies is more prominent in UC. Circulating antibodies against colon epithelial goblet cells have been identified,²⁹ while perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are observed in the majority of active UC patients.^{52,53} Although autoantibodies are the exception rather than the rule in CD patients, anti-GM-CSF antibodies have been described, are associated with severe disease, and may also contribute to the impaired anti-microbial responses by neutrophils and macrophages in the gut.^{54,55}

Bacterial sequencing of IBD stool samples has yielded remarkable insights into the species targeted by IgA, allowing for functional validation of key commensal and pathobiont species, such as *Clostridiales* and *Ruminococcaceae* species in CD and *Eubacterium dolichum* in UC.^{56,57} Future studies will help to resolve microbial species targeted by IgG in IBD patients across disease subclasses.

IgG-genetic interactions

While UC and CD share numerous genetic associations, several major genetic determinants of susceptibility are unique to each subclass (Figure 1). It may therefore be that these differing susceptibility pathways influence the overall role of IgG and FcγR in disease pathogenesis or progression in different ways. Therefore, despite the presence of anti-commensal IgG in CD, and similar levels of FcγR transcript enrichment in CD biopsies relative to

healthy controls as observed in UC (Figure 3), the functional effect is dissimilar because of interactions with other pathogenic pathways at play.

As noted previously, CD is linked to defects in intracellular microbial sensing. Therefore it is of relevance that the FcγRIIA-R131 polymorphism that mediates protection in UC has been associated with susceptibility to a number of infections, including invasive pneumococcal disease,^{58,59} and that IgG and FcγRs play a functional role in defense against mycobacteria, intracellular pathogens.⁶⁰ Therefore, the deleterious effects of FcγRIIA-R131 on bacterial clearance might outweigh its beneficial, anti-inflammatory effects in CD.

In mice, B cells play a critical role in the clearance of *Citrobacter rodentium*, an attaching-effacing enteropathic bacterium widely used to model human IBD pathology. This protection is dually dependent on IgG-FcγR signalling and CD4⁺ T cells, but independent of secretory IgA.^{10,61,62} It is noteworthy that *Nod2*-deficient mice, which are susceptible to *C. rodentium* challenge, exhibit an impaired local anti-microbial IgG response, suggesting local IgG dysfunction may compound invasive bacterial dissemination that precipitates colitis.⁶³ In addition, although anti-microbial IgG is elevated in CD patients, the quality and nature of this response is likely to vary according to individual genetic and environmental factors.

Secondary considerations regarding this differential association arise from the inflammatory networks contributing to CD and UC pathogenesis.⁶⁴ While the IL-23-Th17 axis is central to both IBD subclasses, lamina propria cells

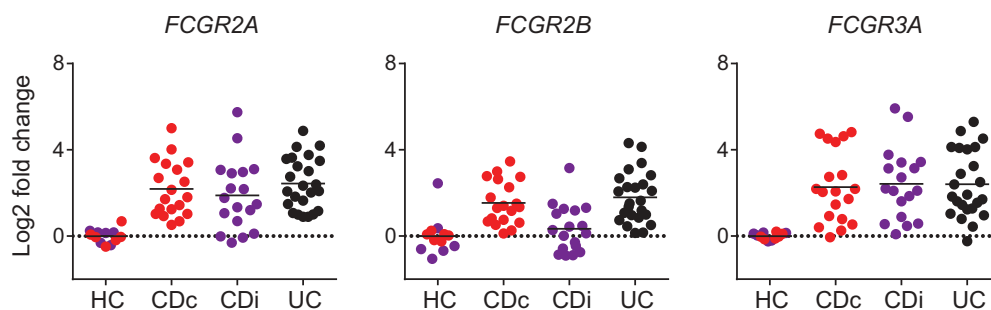


Figure 3. FcγR expression in IBD mucosal biopsies. Transcriptomic analysis of FCGR gene expression in mucosal biopsies from UC (n = 24), colonic CD (CDc; n = 19), and ileal CD (CDi; n = 18) patients and healthy controls (ileum n = 6; colon n = 6). Data generated from GEO: GSE16879.

isolated from CD and UC patients produce excessive levels of IFN γ and IL-13, respectively.^{64,65} In turn, this may impact the consequences of Fc γ R signalling by intestinal immune cell subsets. For example, IFN γ -programmed M1-like macrophages are unaffected by dual-stimulation with TLR and Fc γ R ligands relative to TLR stimulation alone, while M2-like macrophages and DCs exhibit a potent Th17-inducing phenotype in response to IgG-opsonised bacteria.^{66,67} Whether this phenotype translates to intestinal macrophages isolated IBD patients, however, remains to be investigated.

Conclusion

While mucosal IgG responses are common to both UC and CD, significant differences are observed in the targets and inflammatory characteristics of these responses that may impact disease susceptibility. Future studies will be needed to dissect the biological consequences of this heterogeneity *in vivo* and how IgG-targeted therapeutics may be used to greatest effect. Given its role in pathogen defense, Fc γ R blockade may be detrimental in CD by promoting microbial penetrance and dissemination in patients compounded by genetic variants in PRRs or autophagy-related pathways. Conversely, IgG blockade may be a particularly attractive target in severe IBD patients refractory to conventional therapies, where similar interventions, such as intravenous Ig, have shown potential efficacy in the past.

Methods

Publicly available microarray datasets were downloaded from GEO (<https://www.ncbi.nlm.nih.gov/geo/>) along with appropriate chip annotation data. All analyses were carried out using R. All datasets were downloaded as raw intensity matrices. Data was normalized using RMA and limma. Probes were reduced to one probe per gene by selecting the probe with the greatest variance across the samples using the gene filter package.

Acknowledgments

T.C-D. and M.R.C. contributed equally to the manuscript. T.C-D. was supported by a Wellcome Trust Infection,

Immunity, and Inflammation PhD Fellowship. M.R.C. and T.C.D. are supported by a Medical Research Council New Investigator Research Grant (MR/N024907/01). M.R.C is supported by the National Institute for Health Research (NIHR), the NIHR Blood and Transplant Research Unit (NIHR BTRU-2014-10027), and an NIHR Research Professorship (RP-2017-08-ST2-002).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the Medical Research Council [MR/N024907/01]; National Institute for Health Research [RP-2017-08-ST2-002]; National Institute for Health Research [NIHR BTRU-2014-10027].

ORCID

Tomas Castro-Dopico  <http://orcid.org/0000-0002-6964-5478>

References

1. Pabst O. New concepts in the generation and functions of IgA. *Nat Rev Immunol.* 2012;12:821–832. doi:10.1038/nri3322.
2. Fransen F, Zagato E, Mazzini E, Fosso B, Manzari C, El Aidy S, Chiavelli A, D'Erchia AM, Sethi MK, Pabst O, *et al.* BALB/c and C57BL/6 mice differ in polyreactive IgA abundance, which impacts the generation of antigen-specific IgA and microbiota diversity. *Immunity.* 2015;43:527–540. doi:10.1016/j.immuni.2015.08.011.
3. Bollinger RR, Everett ML, Wahl SD, Lee YH, Orndorff PE, Parker W. Secretory IgA and mucin-mediated biofilm formation by environmental strains of *Escherichia coli*: role of type 1 pili. *Mol Immunol.* 2006;43:378–387. doi:10.1016/j.molimm.2005.02.013.
4. Moor K, Diard M, Sellin ME, Felmy B, Wotzka SY, Toska A, Bakkeren E, Arnoldini M, Bansept F, Co AD, *et al.* High-avidity IgA protects the intestine by enchaining growing bacteria. *Nature.* 2017;544:498–502. doi:10.1038/nature22058.
5. Castro-Dopico T, Clatworthy MR. IgG and Fc γ receptors in intestinal immunity and inflammation. *Front Immunol.* 2019;10. doi:10.3389/fimmu.2019.01365.
6. Ohsaki A, Venturelli N, Buccigrosso TM, Osganian SK, Lee J, Blumberg RS, Oyoshi MK. Maternal IgG immune complexes induce food allergen-specific tolerance in offspring. *J Exp Med.* 2017;215:91–113. doi:10.1084/jem.20171163.

7. Koch MA, Reiner GL, Lugo KA, Kreuk LSM, Stanbery AG, Ansaldo E, Seher TD, Ludington WB, Barton GM. Maternal IgG and IgA antibodies dampen mucosal T helper cell responses in early life. *Cell*. 2016;165:827–841. doi:10.1016/j.cell.2016.04.055.
8. Gomez de Agüero M, Ganal-Vonarburg SC, Fuhrer T, Rupp S, Uchimura Y, Li H, Steinert A, Heikenwalder M, Hapfelmeier S, Sauer U, *et al.* The maternal microbiota drives early postnatal innate immune development. *Science (New York, NY)*. 2016;351:1296–1302. doi:10.1126/science.aad2571.
9. Maaser C, Housley MP, Iimura M, Smith JR, Vallance BA, Finlay BB, Schreiber JR, Varki NM, Kagnoff MF, Eckmann L. Clearance of citrobacter rodentium requires B cells but not secretory immunoglobulin A (IgA) or IgM antibodies. *Infect Immun*. 2004;72:3315–3324. doi:10.1128/IAI.72.6.3315-3324.2004.
10. Masuda A, Yoshida M, Shiomi H, Ikezawa S, Takagawa T, Tanaka H, Chinzei R, Ishida T, Morita Y, Kutsumi H, *et al.* Fcγ receptor regulation of citrobacter rodentium infection. *Infect Immun*. 2008;76:1728–1737. doi:10.1128/IAI.01493-07.
11. Caballero-Flores G, Sakamoto K, Zeng MY, Wang Y, Hakim J, Matus-Acuña V, Inohara N, Núñez G. Maternal immunization confers protection to the offspring against an attaching and effacing pathogen through delivery of IgG in breast milk. *Cell Host Microbe*. 2019;25:313–323.e4. doi:10.1016/j.chom.2018.12.015.
12. Yoshida M, Kobayashi K, Kuo TT, Bry L, Glickman JN, Claypool SM, Kaser A, Nagaishi T, Higgins DE, Mizoguchi E, *et al.* Neonatal Fc receptor for IgG regulates mucosal immune responses to luminal bacteria. *J Clin Invest*. 2006;116:2142–2151. doi:10.1172/JCI27821.
13. Kamada N, Sakamoto K, Seo S-U, Zeng MY, Kim Y-G, Cascalho M, Vallance BA, Puente JL, Núñez G. Humoral immunity in the gut selectively targets phenotypically virulent attaching-and-effacing bacteria for intraluminal elimination. *Cell Host Microbe*. 2015;17:617–627. doi:10.1016/j.chom.2015.04.001.
14. Baklien K, Brandtzaeg P. Comparative mapping of the local distribution of immunoglobulin-containing cells in ulcerative colitis and Crohn's disease of the colon. *Clin Exp Immunol*. 1975;22:197–209.
15. Brandtzaeg P, Baklien K, Fausa O, Noel PS. Immunohistochemical characterization of local immunoglobulin formation in ulcerative colitis. *Gastroenterology*. 1974;66:1123–1136.
16. Kaser A, Zeissig S, Blumberg RS. Inflammatory Bowel disease. *Annu Rev Immunol*. 2010;28:573–621. doi:10.1146/annurev-immunol-030409-101225.
17. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876–885. doi:10.1056/NEJMoa030815.
18. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, *et al.* Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *N Engl J Med*. 2010;362:1383–1395. doi:10.1056/NEJMoa0904492.
19. Sandborn WJ, Gasink C, Gao -L-L, Blank MA, Johanss J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, *et al.* Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med*. 2012;367:1519–1528. doi:10.1056/NEJMoa1203572.
20. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, *et al.* Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491:119–124. doi:10.1038/nature11582.
21. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. *Gastroenterology*. 2011;140:1704–1712. doi:10.1053/j.gastro.2011.02.046.
22. Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, *et al.* Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet*. 2007;39:596–604. doi:10.1038/ng2032.
23. Asano K, Matsushita T, Umeno J, Hosono N, Takahashi A, Kawaguchi T, Matsumoto T, Matsui T, Kakuta Y, Kinouchi Y, *et al.* A genome-wide association study identifies three new susceptibility loci for ulcerative colitis in the Japanese population. *Nat Genet*. 2009;41:1325–1329. doi:10.1038/ng.482.
24. Smith KGC, Clatworthy MR. FcγRIIB in autoimmunity and infection: evolutionary and therapeutic implications. *Nat Rev Immunol*. 2010;10:328–343. doi:10.1038/nri2762.
25. Bruhns P, Jönsson F. Mouse and human FcR effector functions. *Immunol Rev*. 2015;268:25–51. doi:10.1111/imr.12350.
26. Castro-Dopico T, Dennison TW, Ferdinand JR, Mathews RJ, Fleming A, Clift D, Stewart BJ, Jing C, Strongili K, Labzin LI, *et al.* Anti-commensal IgG drives intestinal inflammation and type 17 immunity in ulcerative colitis. *Immunity*. 2019;50:1099–1114. e1010. doi:10.1016/j.immuni.2019.02.006.
27. Macpherson A, Khoo UY, Forgacs I, Philpott-Howard J, Bjarnason I. Mucosal antibodies in inflammatory bowel disease are directed against intestinal bacteria. *Gut*. 1996;38:365–375. doi:10.1136/gut.38.3.365.
28. Adams RJ, Heazlewood SP, Gilshenan KS, O'Brien M, McGuckin MA, Florin THJ. IgG antibodies against common gut bacteria are more diagnostic for Crohn's disease than IgG against mannan or flagellin. *Am*

- J Gastroenterol. 2008;103:386–396. doi:10.1111/j.1572-0241.2007.01577.x.
29. Hibi T, Ohara M, Kobayashi K, Brown WR, Toda K, Takaishi H, Hosoda Y, Hayashi A, Iwao Y, Watanabe M. Enzyme linked immunosorbent assay (ELISA) and immunoprecipitation studies on anti-goblet cell antibody using a mucin producing cell line in patients with inflammatory bowel disease. *Gut*. 1994;35:224–230. doi:10.1136/gut.35.2.224.
 30. Lodes MJ, Cong Y, Elson CO, Mohamath R, Landers CJ, Targan SR, Fort M, Hershberg RM. Bacterial flagellin is a dominant antigen in Crohn disease. *J Clin Invest*. 2004;113:1296–1306. doi:10.1172/JCI20295.
 31. Ferrante M, Henckaerts L, Joossens M, Pierik M, Joossens S, Dotan N, Norman GL, Altstock RT, Van Steen K, Rutgeerts P, *et al*. New serological markers in inflammatory bowel disease are associated with complicated disease behaviour. *Gut*. 2007;56:1394–1403. doi:10.1136/gut.2006.108043.
 32. Benckert J, Schmolka N, Kreschel C, Zoller MJ, Sturm A, Wiedenmann B, Wardemann H. The majority of intestinal IgA + and IgG + plasmablasts in the human gut are antigen-specific. *J Clin Invest*. 2011;121:1946–1955. doi:10.1172/JCI44447.
 33. Rosekrans PCM, Meijer CJLM, van der Wal AM, Cornelisse CJ, Lindeman J. Immunoglobulin containing cells in inflammatory bowel disease of the colon: A morphometric and immunohistochemical study. *Gut*. 1980;21:941–947. doi:10.1136/gut.21.11.941.
 34. Scott BB, Goodall A, Stephenson P, Jenkins D. Rectal mucosal plasma cells in inflammatory bowel disease. *Gut*. 1983;24:519–524. doi:10.1136/gut.24.6.519.
 35. Ruthlein J, Ibe M, Burghardt W, Mossner J, Auer IO. Immunoglobulin G (IgG), IgG1, and IgG2 determinations from endoscopic biopsy specimens in control, Crohn's disease, and ulcerative colitis subjects. *Gut*. 1992;33:507–512. doi:10.1136/gut.33.4.507.
 36. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, *et al*. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet*. 2008;40:955–962. doi:10.1038/ng.175.
 37. Weersma RK, Crusius JB, Roberts RL, Koeleman BP, Palomino-Morales R, Wolfkamp S, Hollis-Moffatt JE, Festen EA, Meisneris S, Heijmans R, *et al*. Association of FcγR2a, but not FcγR3a, with inflammatory bowel diseases across three Caucasian populations. *Inflamm Bowel Dis*. 2010;16:2080–2089. doi:10.1002/ibd.21342.
 38. Latiano A, Palmieri O, Valvano MR, Bossa F, Latiano T, Corritore G, DeSanto E, Andriulli A, Annese V. Evaluating the role of the genetic variations of PTPN22, NFKB1, and FcγRIIIA genes in inflammatory bowel disease: a meta-analysis. *Inflamm Bowel Dis*. 2007;13:1212–1219. doi:10.1002/ibd.20185.
 39. Uo M, Hisamatsu T, Miyoshi J, Kaito D, Yoneno K, Kitazume MT, Mori M, Sugita A, Koganei K, Matsuoka K, *et al*. Mucosal CXCR4+ IgG plasma cells contribute to the pathogenesis of human ulcerative colitis through FcγR-mediated CD14 macrophage activation. *Gut*. 2013;62:1734–1744. doi:10.1136/gutjnl-2012-303063.
 40. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. *Front Immunol*. 2014;5:1–17. doi:10.3389/fimmu.2014.00001.
 41. Kett K, Rognum TO, Brandtzaeg P. Mucosal subclass distribution of immunoglobulin G-producing cells is different in ulcerative colitis and Crohn's disease of the colon. *Gastroenterology*. 1987;93:919–924. doi:10.1016/0016-5085(87)90552-x.
 42. Scott MG, Nahm MH, Macke K, Nash GS, Bertovich MJ, MacDermott RP. Spontaneous secretion of IgG subclasses by intestinal mononuclear cells: differences between ulcerative colitis, Crohn's disease, and controls. *Clin Exp Immunol*. 1986;66:209–215.
 43. Theodoratou E, Campbell H, Ventham NT, Kolarich D, Pučić-Baković M, Zoldoš V, Fernandes D, Pemberton IK, Rudan I, Kennedy NA, *et al*. The role of glycosylation in IBD. *Nat Rev Gastroenterol Hepatol*. 2014;11:588–600. doi:10.1038/rgastro.2014.78.
 44. Nimmerjahn F, Ravetch JV. Divergent immunoglobulin g subclass activity through selective Fc receptor binding. *Science*. 2005;310:1510–1512. doi:10.1126/science.1118948.
 45. Lauc G, Huffman JE, Pučić M, Zgaga L, Adamczyk B, Mužinić A, Novokmet M, Polašek O, Gornik O, Krištić J, *et al*. Loci associated with N-glycosylation of human immunoglobulin G show pleiotropy with autoimmune diseases and haematological cancers. *PLoS Genet*. 2013;9:e1003225–e1003225. doi:10.1371/journal.pgen.1003225.
 46. Shinzaki S, Iijima H, Nakagawa T, Egawa S, Nakajima S, Ishii S, Irie T, Kakiuchi Y, Nishida T, Yasumaru M, *et al*. IgG oligosaccharide alterations are a novel diagnostic marker for disease activity and the clinical course of inflammatory bowel disease. *Am J Gastroenterol*. 2008;103:1173–1181. doi:10.1111/j.1572-0241.2007.01699.x.
 47. Dubé R, Rook GAW, Steele J, Brealey R, Dwek R, Rademacher T, Lennard-Jones J. Agalactosyl IgG in inflammatory bowel disease: correlation with C-reactive protein. *Gut*. 1990;31:431–434. doi:10.1136/gut.31.4.431.
 48. Trbojević Akmačić I, Ventham NT, Theodoratou E, Vučković F, Kennedy NA, Krištić J, Nimmo ER, Kalla R, Drummond H, Štambuk J, *et al*. Inflammatory bowel disease associates with proinflammatory potential of the immunoglobulin G glycome. *Inflamm Bowel Dis*. 2015;21:1237–1247. doi:10.1097/MIB.0000000000000268.

49. Landers CJ, Cohavy O, Misra R, Yang H, Lin YC, Braun J, Targan SR. Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. *Gastroenterology*. 2002;123:689–699. doi:10.1053/gast.2002.35379.
50. Sendid B, Colombel JF, Jacquinet PM, Faille C, Fruit J, Cortot A, Lucidarme D, Camus D, Poulain D. Specific antibody response to oligomannosidic epitopes in Crohn's disease. *Clin Diagn Lab Immunol*. 1996;3:219–226.
51. Quinton JF, Sendid B, Reumaux D, Duthilleul P, Cortot A, Grandbastien B, Charrier G, Targan SR, Colombel JF, Poulain D. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut*. 1998;42:788–791. doi:10.1136/gut.42.6.788.
52. Teegen B, Niemann S, Probst C, Schlumberger W, Stöcker W, Komorowski L. DNA-bound lactoferrin is the major target for antineutrophil perinuclear cytoplasmic antibodies in ulcerative colitis. *Ann N Y Acad Sci*. 2009;1173:161–165. doi:10.1111/j.1749-6632.2009.04752.x.
53. Seibold F, Weber P, Klein R, Berg PA, Wiedmann KH. Clinical significance of antibodies against neutrophils in patients with inflammatory bowel disease and primary sclerosing cholangitis. *Gut*. 1992;33:657–662. doi:10.1136/gut.33.5.657.
54. Han X, Uchida K, Jurickova I, Koch D, Willson T, Samson C, Bonkowski E, Trauernicht A, Kim MO, Tomer G, *et al.* Granulocyte-macrophage colony-stimulating factor autoantibodies in murine ileitis and progressive ileal Crohn's disease. *Gastroenterology*. 2009;136(1261–1271):e1261–1263. doi:10.1053/j.gastro.2008.12.046.
55. Gathungu G, Kim M-O, Ferguson JP, Sharma Y, Zhang W, Ng SME, Bonkowski E, Ning K, Simms LA, Croft AR, *et al.* Granulocyte-macrophage colony-stimulating factor autoantibodies: a marker of aggressive Crohn's disease. *Inflamm Bowel Dis*. 2013;19:1671–1680. doi:10.1097/MIB.0b013e318281f506.
56. Palm NW, de Zoete MR, Cullen TW, Barry NA, Stefanowski J, Hao L, Degnan PH, Hu J, Peter I, Zhang W, *et al.* Immunoglobulin a coating identifies colitogenic bacteria in inflammatory bowel disease. *Cell*. 2014;158:1000–1010. doi:10.1016/j.cell.2014.08.006.
57. Viladomiu M, Kivolowitz C, Abdulhamid A, Dogan B, Victorio D, Castellanos JG, Woo V, Teng F, Tran NL, Sczesnak A, *et al.* IgA-coated E. coli enriched in Crohn's disease spondyloarthritis promote TH17-dependent inflammation. *Sci Transl Med*. 2017;9. doi:10.1126/scitranslmed.aaf9655.
58. Willcocks LC, Smith KG, Clatworthy MR. Low-affinity Fcγ receptors, autoimmunity and infection. *Expert Rev Mol Med*. 2009;11:e24. doi:10.1017/S1462399409001161.
59. Clatworthy MR. Fcγ receptor polymorphisms and susceptibility to infection. In: Ackerman MENF editor. *Antibody Fc linking adaptive and innate immunity*. Cambridge (MA): Academic Press, Elsevier; 2014. p. 217–238.
60. Lu LL, Chung AW, Rosebrock TR, Ghebremichael M, Yu WH, Grace PS, Schoen MK, Tafesse F, Martin C, Leung V, *et al.* A functional role for antibodies in tuberculosis. *Cell*. 2016;167:433–443 e414. doi:10.1016/j.cell.2016.08.072.
61. Bry L, Brenner MB. Critical role of T cell-dependent serum antibody, but not the gut-associated lymphoid tissue, for surviving acute mucosal infection with *Citrobacter rodentium*, an attaching and effacing pathogen. *J Immunol*. 2004;172:433–441. doi:10.4049/jimmunol.172.1.433.
62. Simmons CP, Clare S, Ghaem-Maghami M, Uren TK, Rankin J, Huett A, Goldin R, Lewis DJ, MacDonald TT, Strugnell RA, *et al.* Central role for B lymphocytes and CD4+ T cells in immunity to infection by the attaching and effacing pathogen *Citrobacter rodentium*. *Infect Immun*. 2003;71:5077–5086. doi:10.1128/iai.71.9.5077-5086.2003.
63. Kim YG, Kamada N, Shaw MH, Warner N, Chen GY, Franchi L, Núñez G. The Nod2 sensor promotes intestinal pathogen eradication via the chemokine CCL2-dependent recruitment of inflammatory monocytes. *Immunity*. 2011;34:769–780. doi:10.1016/j.immuni.2011.04.013.
64. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol*. 2014;14:329–342. doi:10.1038/nri3661.
65. Heller F, Florian P, Bojarski C, Richter J, Christ M, Hillenbrand B, Mankertz J, Gitter AH, Bürgel N, Fromm M, *et al.* Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology*. 2005;129:550–564. doi:10.1016/j.gastro.2005.05.002.
66. den Dunnen J, Vogelpoel LTC, Wypych T, Muller FJM, de Boer L, Kuijpers TW, Zaat SAJ, Kapsenberg ML, de Jong EC. IgG opsonization of bacteria promotes Th17 responses via synergy between TLRs and FcγRIIIa in human dendritic cells. *Blood*. 2012;120:112–121. doi:10.1182/blood-2011-12-399931.
67. Vogelpoel LTC, Hansen IS, Rispens T, Muller FJM, van Capel TMM, Turina MC, Vos JB, Baeten DLP, Kapsenberg ML, de Jong EC, *et al.* Fc gamma receptor-TLR cross-talk elicits pro-inflammatory cytokine production by human M2 macrophages. *Nat Commun*. 2014;5:5444. doi:10.1038/ncomms6444.