

New Tricks of Our Old Friend the Glucocorticoid Receptor



From Combating Ulcerative Colitis to Preventing Associated Colorectal Cancer

Ulcerative colitis is the most common form of inflammatory bowel disease (IBD) and a major risk factor for the development of colorectal cancer.¹ Synthetic glucocorticoids are essential drugs in combatting inflammatory diseases and mediate their anti-inflammatory actions by binding the glucocorticoid receptor (GR). Despite its clinical importance, prolonged glucocorticoid treatment is hampered by the emergence of glucocorticoid resistance and detrimental side effects.² Therefore, it is crucial to optimize glucocorticoid use in IBD, which requires an improved understanding of the glucocorticoid action in IBD.

Because GR is ubiquitously expressed, glucocorticoids can affect different cell types in the colon, including immune cells and intestinal epithelial cells (IECs). Using a dextran sulfate sodium (DSS)-induced colitis model, GR deletion in myeloid cells was shown to inhibit the resolution (but not the acute) phase of the disease, which was accompanied by increased infiltration of macrophages and proinflammatory cytokine expression in the colon.³ Yet, for ulcerative colitis the role of GR in IECs has remained largely unresolved.

Earlier work showed that GR deletion in IECs coincided with transient upregulation of proinflammatory chemokines and cytokines in basal conditions,⁴ but an inflammatory or tumorigenic context was not considered. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, the group of Reichardt took a more direct approach and used both a DSS-induced colitis model and a colitis-associated colorectal cancer model, in which the intestinal epithelial GR was inducibly deleted (GR^{villin} mice), to investigate GR action in IECs.⁵ These authors showed that DSS-induced colitis was clearly exacerbated in GR^{villin} mice compared with GR^{flox} mice that still express wild-type GR. More specifically, GR^{villin} mice displayed decreased body weight, worse clinical disease score, reduced colon length, and increased serum interleukin-6 levels compared with GR^{flox} mice. This is further supported by their findings that compared with GR^{flox} mice, GR^{villin} mice showed both aggravated DSS-induced tissue damage, and an even further compromised epithelial barrier integrity.

Diving deeper into the mechanistic basis of the aggravated colitis in GR^{villin} mice, Reichardt and colleagues further studied the gene expression profile of IEC isolated from colon.⁵ Several chemokines (*Cxcl1*, *Cxcl5*, *Ccl5*) that are involved in the pathogenesis of colitis and attract immune cells, such as neutrophils and monocytes, were only upregulated in IEC of DSS-treated GR^{flox} mice, suggesting that GR triggers chemokine induction in IEC during inflammation, a proinflammatory action that has been reported before.⁶ In contrast, genes important for the control of the epithelial barrier integrity (*Tnfr2* and *Mlck*) or pathogen sensing

(*Tlr4*) were overexpressed in IECs of GR-devoid GR^{villin} mice, but not in functional GR-expressing GR^{flox} mice, indicating GR is required for the repression of these genes. Together this suggests that endogenous glucocorticoids safeguard epithelial permeability and block pattern recognition receptor expression in IECs via binding to an IEC-expressed GR, hereby limiting proinflammatory nuclear factor- κ B signaling.

Because chemokine expression was reduced in IEC of DSS-treated GR^{villin} mice, a logical next step was to investigate how this affected myeloid cell infiltration. In line with the gene expression results, a reduced number of neutrophils, total and inflammatory macrophages, were found in the lamina propria of DSS-treated GR^{villin} mice compared with GR^{flox} mice.⁵ This important finding indicates that GR expression in IEC influences recruitment of myeloid cells in the inflamed colon. To link this with the observed aggravated colitis in GR^{villin} mice, a proinflammatory gene expression analysis was performed in lamina propria cells. Remarkably, chemokine and cytokine expression levels were all strongly upregulated in lamina propria cells of GR^{villin} mice compared with GR^{flox} mice, indicative of hyperactivated lamina propria cells.⁵

Because DSS-induced colitis was exacerbated in GR^{villin} mice, the team of Reichardt further showed that this also influenced tumorigenesis by using the carcinogen azoxymethane.⁵ In a DSS/azoxymethane model, both the number and size of the developed tumors was strongly increased in GR^{villin} mice compared with GR^{flox} mice, although not linked to changes in leukocyte infiltration.⁵ In an elegant experiment where colitis and tumorigenesis were induced before GR was deleted in IEC, the severity of colitis and the number and size of the developed tumors showed to be comparable in both genotypes.⁵ This clearly confirmed that the aggravated colitis, and not the deleted GR in IECs, caused the enhanced tumorigenesis. The role of GR in tumorigenesis remains clinically relevant, not least because of the long-term glucocorticoid use to relieve chemotherapy-associated symptoms and perioperative to cancer surgery,⁷ but also because of the ongoing debate concerning the role of glucocorticoids in various solid cancers.^{8,9}

This study greatly advances the understanding of GR functioning in the colon and highlights that GR's transcriptional activation and repression mechanisms¹⁰ are involved to control gene expression in IECs. Further questions remain to be resolved. For instance, how would the inducible expression of GR (dimerization) mutants steer these alterations against a GRwt null background? Does GR expression change over time in IECs of patient samples and does this GR remain functional? Notwithstanding these open questions,

Reichardt and colleagues clarified that GR action not only keeps the inflammatory response in colitis under control, but may also directly impact the progression toward colorectal cancer. In extension, optimizing glucocorticoid treatment and delivery strategies in patients may even decrease the risk of developing colitis-associated colorectal cancer, highlighting once more the importance of glucocorticoids and maintaining a functional GR in the treatment of IBD.

DORIEN CLARISSE, PhD

Translational Nuclear Receptor Research
VIB Center for Medical Biotechnology
Ghent, Belgium
Department of Biomolecular Medicine, Ghent University
Ghent, Belgium
Cancer Research Institute Ghent
Ghent, Belgium

ILSE M. BECK, PhD

Department of Health Sciences
Odisee University College
Ghent, Belgium

References

1. Olén O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, Ekborn A, Sørensen HT, Ludvigsson JF. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. *Lancet* 2020;395:123–131.
2. Clarisse D, Offner F, De Bosscher K. Latest perspectives on glucocorticoid-induced apoptosis and resistance in lymphoid malignancies. *Biochim Biophys Acta* 2020;1874:188430.
3. Meers GK, Bohnenberger H, Reichardt HM, Lühder F, Reichardt SD. Impaired resolution of DSS-induced colitis in mice lacking the glucocorticoid receptor in myeloid cells. *PLoS One* 2018;13:e0190846.
4. Aranda CJ, Arredondo-Amador M, Ocón B, Lavín JL, Aransay AM, Martínez-Augustin O, De Medina FS. Intestinal epithelial deletion of the glucocorticoid receptor NR3C1 alters expression of inflammatory mediators and barrier function. *FASEB J* 2019;33:14067–14082.
5. Muzzi C, Watanabe N, Twomey E, Meers GK, Reichardt HM, Bohnenberger H, Reichardt SD. The glucocorticoid receptor in intestinal epithelial cells alleviates colitis and associated colorectal cancer in mice. *Cell Mol Gastroenterol Hepatol* 2021;11:1505–1518.
6. Escoter-Torres L, Caratti G, Mechtidou A, Tuckermann J, Uhlenhaut NH, Vettorazzi S. Fighting the fire: mechanisms of inflammatory gene regulation by the glucocorticoid receptor. *Front Immunol* 2019;10:1–17.
7. McSorley ST, Dolan RD, Roxburgh CS, Horgan PG, MacKay GJ, McMillan DC. Possible dose dependent effect of perioperative dexamethasone and laparoscopic surgery on the postoperative systemic inflammatory response and complications following surgery for colon cancer. *Eur J Surg Oncol* 2019;45:1613–1618.
8. Chen Z, Lan X, Wu D, Sunkel B, Ye Z, Huang J, Liu Z, Clinton SK, Jin VX, Wang Q. Ligand-dependent genomic function of glucocorticoid receptor in triple-negative breast cancer. *Nature Commun* 2015;6:8323.
9. Kach J, Long TM, Selman P, Tonsing-Carter EY, Bacalao MA, Lastra RR, de Wet L, Comiskey S, Gillard M, VanOpstall C, West DC, Chan W-C, Vander Griend D, Conzen SD, Szmulewitz RZ. Selective glucocorticoid receptor modulators (SGRMs) delay castrate-resistant prostate cancer growth. *Mol Cancer Ther* 2017;16:1680–1692.
10. Van Moortel L, Gevaert K, De Bosscher K. Improved glucocorticoid receptor ligands: fantastic beasts, but how to find them? *Front Endocrinol* 2020;11:559673.

Correspondence

Address correspondence to: Ilse M. Beck, PhD, Department of Health Sciences, Odisee University College, Gebroeders De Smetstraat 1, 9000 Gent, Belgium. e-mail: Ilse.Beck@odisee.be.

Conflicts of interest

The authors disclose no conflicts.



Most current article

© 2021 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2352-345X

<https://doi.org/10.1016/j.jcmgh.2021.02.005>