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EDITORIAL

Targeting SOCE in Intestinal Epithelial Cells: A New Treatment Concept for Inflammatory Bowel Disease?

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal system and its incidence is rising worldwide.[1] Current concepts of the pathogenesis of IBD suggests that IBD is predominantly triggered by environmental factors in genetically susceptible individuals, ultimately resulting in impaired immune cell homeostasis and deterred intestinal epithelial barrier functions by enterocytes and goblets cells.[2-4] Current treatment of IBD consists of tumor necrosis factor blockers, integrin inhibitors, JAK-inhibitors, and interleukin 12/23 blocking antibodies, which predominantly inhibit immune cell activation and function.[5] In contrast, no treatment is currently available that would effectively improve epithelial barrier functions in intestinal inflammation by targeting epithelium intrinsic pathways. As a large proportion of patients with IBD does not sufficiently respond to available biologics, new treatment concepts are urgently required. To date, the molecular pathways regulating the differentiation, function, and survival of enterocytes and goblet cells are incompletely understood and deeper insights into mechanisms controlling apoptosis in intestinal epithelial cells (IEC) during chronic inflammation are lacking. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Liang et al[4] provide evidence that the stromal interaction molecule (STIM), which controls Store-operated Ca^{2+} entry (SOCE), may be a pertinent molecule to target in epithelial cells.

SOCE, mediated by calcium release activated channels (CRAC) and STIM proteins, represents the predominant Ca^{2+} influx pathway in lymphocytes but can also be observed in a large variety of other cells including enterocytes and goblet cells.[4,6,7] Activation of SOCE can be detected on agonist stimulation of various surface receptors on the plasma membrane of cells, such as the T cell receptor on T cells[7] or the acetylcholine receptor on neural cells[8] inducing a phospholipase C–dependent production of inositol 1,4,5-trisphosphate (IP_3). Subsequently, IP_3 binds to and opens the IP_3 receptors located on the membrane of the endoplasmic reticulum (ER), resulting in a transient release of Ca^{2+} from the ER into the cytoplasm.[9] The consecutive decrease in ER Ca^{2+} concentrations is sensed by N-terminal EF-hand motifs of ER-based STIM1 and STIM2 proteins,[10] inducing their oligomerization and translocation to the plasma membrane, where they bind to ORAI1-CRAC channels resulting in sustained influx of extracellular Ca^{2+} into the cytoplasm.[11] SOCE not only controls the activation of transcription factors, such as NFAT, but also regulates multiple cellular functions including mitochondrial activation, apoptosis, and trafficking of cellular vesicles.[6,7] The importance of SOCE is highlighted by patients with loss-of-function mutations in *STIM1* or *ORAI1*, who suffer from immunodeficiency, muscular hypotonia, and impaired enamel formation.[12-14]

Liang et al[4] now identify the SOCE-signaling component STIM1 as an important modulator of intestinal epithelial barrier functions during intestinal inflammation. Thus, the authors showed that STIM1 expression is increased in IEC of inflamed tissues from patients with IBD. The authors next developed mice with a conditional genetic deletion of *Stim1* in IEC to investigate the impact of decreased SOCE-activity on IEC function. Remarkably, the deletion of STIM1 in IEC had no impact on epithelial differentiation and gut homeostasis at steady state.[4] In contrast, on induction of acute or chronic dextran sulfate sodium colitis, $Stim1^{\Delta IEC}$ mice displayed reduced disease severity, decreased inflammation, and improved epithelial regeneration. This effect could be traced back to reduced loss of goblet cells during the inflammatory phase of dextran sulfate sodium colitis and, subsequently, to faster epithelial reconstitution. Remarkably, increased protection of the epithelial barrier in STIM1-deficient mice under inflammatory conditions was paralleled by an increased expression of tight junction proteins. Furthermore, Liang et al[4] observed an augmented survival of goblet cells in the acute phase of dextran sulfate sodium, caused by decreased levels of intracellular Ca^{2+} and reduced ER stress, leading to an increased production of mucin by goblet cells and an enhanced thickness of the intestinal mucus layer, ultimately reducing the translocation of commensal bacteria in $Stim1^{\Delta IEC}$ mice.

Because Liang et al[4] detected increased expression of STIM1 in IEC and in lamina propria mononuclear cells in inflamed tissue of patients with IBD, one may anticipate a beneficial dual effect of the pharmacologic blockade of SOCE in IBD. On the one hand, blocking SOCE might decrease the decay of goblet cells by reducing ER stress under inflammatory conditions, stabilize the inner mucus layer, and prevent bacterial translocation.[4] On the other hand, inhibition of SOCE might suppress effector functions of proinflammatory lymphocytes in IBD. Thus, STIM1-deficient T cells display impaired production of interleukin-17, tumor necrosis factor-α, and interferon-γ and fail to induce colitis in mice.[15] In regard of ongoing clinical trials testing the SOCE-inhibitor Auxora in the treatment of overwhelming immunity in COVID-19 and its promising safety profiles,[16] the application of SOCE-inhibitors might represent a new concept for treating IBD.

RAINER GLAUBEN, PhD
MARILENA LETIZIA, MSc
Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin
Department of Gastroenterology, Infectious Diseases and Rheumatology
Campus Benjamin Franklin
Berlin, Germany

CARL WEIDINGER, MD
Charité – Universitätsmedizin Berlin
corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin
Department of Gastroenterology
Infectious Diseases and Rheumatology
Institute of Health at Charité – Universitätsmedizin Berlin
Clinician Scientist Program
Berlin, Germany

References

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.e42; quiz e30.
2. Parikh K, Antanaviciute A, Fawkner-Corbett D, Jagielowicz M, Aulicino A, Lagerholm C, Davis S, Kinchen J, Chen HH, Alham NK, Ashley N, Johnson E, Hublitz P, Bao L, Lukomska J, Andev RS, Bjorklund E, Kessler BM, Fischer R, Goldin R, Koohy H, Simmons A. Colonic epithelial cell diversity in health and inflammatory bowel disease. Nature 2019;567:49–55.
3. McCauley HA, Guasch G. Three cheers for the goblet cell: maintaining homeostasis in mucosal epithelia. Trends Mol Med 2015;21:492–503.
4. Liang X, Xie J, Liu H, Zhao R, Zhang W, Wang H, Pan H, Zhou Y, Han W. STIM1 Deficiency In Intestinal Epithelium Attenuates Colonic Inflammation and Tumorigenesis by Reducing ER Stress of Goblet Cells. Cell Mol Gastroenterol Hepatol 2022;14:193–217.
5. Neurath MF. Targeting immune cell circuits and trafficking in inflammatory bowel disease. Nature immunology 2019;20:970–979.
6. Vaeth M, Kahlfuss S, Feske S. CRAC Channels and Calcium Signaling in T Cell-Mediated Immunity. Trends in immunology 2020.
7. Bergmeier W, Weidinger C, Zee I, Feske S. Emerging roles of store-operated Ca(2)(+) entry through STIM and ORAI proteins in immunity, hemostasis and cancer. Channels (Austin, Tex) 2013;7:379–391.
8. Somasundaram A, Shum AK, McBride HJ, Kessler JA, Feske S, Miller RJ, Prakriya M. Store-operated CRAC channels regulate gene expression and proliferation in neural progenitor cells. The Journal of neuroscience: the official journal of the Society for Neuroscience 2014; 34:9107–9123.
9. Taylor CW, Rahman T, Tovey SC, Dedos SG, Taylor EJ, Velamakanni S. IP3 receptors: some lessons from DT40 cells. Immunol Rev 2009;231:23–44.
10. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE Jr, Meyer T. STIM is a Ca2+ sensor essential for Ca2+-store-depletion-triggered Ca2+ influx. Curr Biol 2005;15:1235–1241.
11. Prakriya M, Feske S, Gwack Y, Srikanth S, Rao A, Hogan PG. Orai1 is an essential pore subunit of the CRAC channel. Nature 2006;443:230–233.
12. Picard C, McCarl CA, Papolos A, Khalil S, Luthy K, Hivroz C, LeDeist F, Rieux-Laucat F, Rechavi G, Rao A, Fischer A, Feske S. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. The New England journal of medicine 2009;360:1971–1980.
13. Fuchs S, Rensing-Ehl A, Speckmann C, Bengsch B, Schmitt-Graeff A, Bondzio I, Maul-Pavicic A, Bass T, Vraetz T, Strahm B, Ankermann T, Benson M, Caliebe A, Folster-Holst R, Kaiser P, Thimme R, Schamel WW, Schwarz K, Feske S, Ehl S. Antiviral and regulatory T cell immunity in a patient with stromal interaction molecule 1 deficiency. Journal of immunology 2012; 188:1523–1533.
14. Kahlfuss S, Kaufmann U, Concepcion AR, Noyer L, Raphael D, Vaeth M, Yang J, Pancholi P, Maus M, Muller J, Kozhaya L, Khodadadi-Jamayran A, Sun Z, Shaw P, Unutmaz D, Stathopulos PB, Feist C, Cameron SB, Turvey SE, Feske S. STIM1-mediated calcium influx controls antifungal immunity and the metabolic function of non-pathogenic Th17 cells. EMBO molecular medicine 2020;12:e11592.
15. McCarl CA, Khalil S, Ma J, Oh-hora M, Yamashita M, Roether J, Kawasaki T, Jairaman A, Sasaki Y, Prakriya M, Feske S. Store-operated Ca2+ entry through ORAI1 is critical for T cell-mediated autoimmunity and allograft rejection. Journal of immunology 2010; 185:5845–5858.
16. Miller J, Bruen C, Schnaus M, Zhang J, Ali S, Lind A, Stoecker Z, Stauderman K, Hebbar S. Auxora versus standard of care for the treatment of severe or critical COVID-19 pneumonia: results from a randomized controlled trial. Critical care (London, England) 2020;24(1):502.

Correspondence
Address correspondence to: Carl Weidinger, MD, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Medizinische Klinik für Gastroenterologie, Infektiologie und Rheumatologie, Hindenburgdamm 30, 12200 Berlin, Germany. e-mail: carl.weidinger@charite.de.

Conflicts of interest
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