



## Review

# Drug Targeting of Inflammatory Bowel Diseases by Biomolecules

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**Table S1.** Main IBD-associated comorbidities.

| Comorbidity   | Main appointed cause(s)  | Known prevalence   | Ref.        |
|---|--|--|-------------|
| Chronic fatigue                                       | Nutritional deficiencies; anaemia; hormonal disturbances; poor sleep quality; psychological aspects; drug side effects | 60–80% (active IBD)<br>20–40% (remitted IBD)                         | [1,2]       |
| Infections  | Old-age susceptibility; anti-TNF therapy; IM therapy; polypharmacy; other associated comorbidities                     | 39.8% (pneumonia)<br>13.2% (sepsis)<br>12.9% (candidiasis)           | [39,73, 74] |
| Psychological disorders (stress, anxiety; depression) | Increased expression of TNF- $\alpha$ and IL-6 proinflammatory cytokines; high levels of CRP                           | 34.3% (depression)<br>18.6% (anxiety)                                | [3–7]       |
| Osteoporosis  | Steroid treatment; systemic inflammation; calcium and vitamin D deficiencies; malnutrition                             | 14–42%   | [8,9]       |
| NAFLD   | Increased expression of IL-6 and TNF- $\alpha$   | 27.5%  | [74,10–12]  |
| PS  | Anti-TNF treatment; T cell misbalance induced by $\alpha 4\beta 7$ blockade  | 2–9%   | [13,14]     |
| Thromboembolism                                       | Inflammation; immobility; surgery; steroid therapy; central venous catheters   | 1–6.7%   | [15–17]     |
| AD; vascular dementia; unspecified dementia           | -  | 1.9% (AD)<br>0.7% (vascular dementia)<br>2.9% (unspecified dementia) | [18–20]     |
| Microvascular dysfunction                             | Diminished vasodilatory capacity to ACh  | -  | [17,21]     |

|                   |  |   |         |
|-------------------|--|---|---------|
| CAD               | High levels of TNF- $\alpha$ and IL-6;<br>High levels of CRP, homocysteine and CD40 ligand | - | [71,22] |
| CVA               | Increased thickness of the carotid intimal-media   | - | [17,23] |
| PD                | Increased expression TNF- $\alpha$ and IL-1 $\beta$  | - | [24–27] |
| MS                | -  | - | [28,29] |
| Obesity           | -  | - | [74,30] |
| Diabetes mellitus | Increased expression of TNF- $\alpha$  | - | [74,31] |
| COPD              | Increased expression of TNF- $\alpha$ , IL-6 and IL-13                                     | - | [32–35] |

<sup>1</sup> Abbreviations: Ach: Acetylcholinesterase; AD: Alzheimer's disease; CAD: Coronary artery disease; CNS: Central Nervous System; COPD: Chronic obstructive pulmonary disease; CVA: Cerebrovascular accidents; IM: Immunomodulators; IBD: Inflammatory Bowel Disease; MS: Multiple sclerosis; NAFLD: Non-alcoholic fatty liver disease; PD: Parkinson's disease; PS: Paradoxical Psoriasis; ROS: Reactive oxygen species.

## Reference

- Hindryckx, P.; Laukens, D.; D'Amico, F.; Danese, S. Unmet Needs in IBD: The Case of Fatigue. *Clin. Rev. Allergy Immunol.* **2018**, *55*, 368–378, doi:10.1007/s12016-017-8641-4.
- Tsai, S.Y.; Chen, H.J.; Lio, C.F.; Kuo, C.F.; Kao, A.C.; Wang, W.S.; Yao, W.C.; Chen, C.; Yang, T.Y. Increased risk of chronic fatigue syndrome in patients with inflammatory bowel disease: A population-based retrospective cohort study. *J. Transl. Med.* **2019**, *17*, 55, doi:10.1186/s12967-019-1797-3.
- Bernstein, C.N. The Brain-Gut Axis and Stress in Inflammatory Bowel Disease. *Gastroenterol. Clin. N. Am.* **2017**, *46*, 839–846, doi:10.1016/j.gtc.2017.08.006.
- Kéri, S.; Szabó, C.; Kelemen, O. Expression of Toll-Like Receptors in peripheral blood mononuclear cells and response to cognitive-behavioral therapy in major depressive disorder. *Brain Behav. Immun.* **2014**, *40*, 235–243, doi:10.1016/j.bbi.2014.03.020.
- Marrie, R.A.; Walld, R.; Bolton, J.M.; Sareen, J.; Walker, J.R.; Patten, S.B.; Singer, A.; Lix, L.M.; Hitchon, C.A.; El-Gabalawy, R.; et al. Rising incidence of psychiatric disorders before diagnosis of immune-mediated inflammatory disease. *Epidemiol. Psychiatr. Sci.* **2019**, *28*, 333–342, doi:10.1017/S2045796017000579.
- Ohlsson, L.; Gustafsson, A.; Lavant, E.; Suneson, K.; Brundin, L.; Westrin, Å.; Ljunggren, L.; Lindqvist, D. Leaky gut biomarkers in depression and suicidal behavior. *Acta Psychiatr. Scand.* **2019**, *139*, 185–193, doi:10.1111/acps.12978.
- Sun, Y.; Li, L.; Xie, R.; Wang, B.; Jiang, K.; Cao, H. Stress Triggers Flare of Inflammatory Bowel Disease in Children and Adults. *Front. Pediatr.* **2019**, *7*, 432, doi:10.3389/fped.2019.00432.
- Farraye, F.A.; Melmed, G.Y.; Lichtenstein, G.R.; Kane, S.V. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. *Am. J. Gastroenterol.* **2017**, *112*, 241–258, doi:10.1038/ajg.2016.537.
- Oh, H.; Ryu, K.; Park, B.; Yoon, B. Osteoporosis and Osteoporotic Fractures in Gastrointestinal Disease. *J. Bone Metab.* **2018**, *25*, 213–217, doi:10.11005/jbm.2018.25.4.213.
- Mundi, M.S.; Velapati, S.; Patel, J.; Kellogg, T.A.; Abu Dayyeh, B.K.; Hurt, R.T. Evolution of NAFLD and Its Management. *Nutr. Clin. Pract.* **2020**, *35*, 72–84, doi:10.1002/ncp.10449.
- Parthasarathy, G.; Revelo, X.; Malhi, H. Pathogenesis of Nonalcoholic Steatohepatitis: An Overview. *Hepatol. Commun.* **2020**, *4*, 478–492, doi:10.1002/hep4.1479.
- Zou, Z.Y.; Shen, B.; Fan, J.G. Systematic Review with Meta-analysis: Epidemiology of Nonalcoholic Fatty Liver Disease in Patients with Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* **2019**, *25*, 1764–1772, doi:10.1093/ibd/izz043.
- Cottone, M.; Sapienza, C.; Macaluso, F.S.; Cannizzaro, M. Psoriasis and Inflammatory Bowel Disease. *Dig. Dis.* **2019**, *37*, 451–457, doi:10.1159/000500116.
- Vlachos, C.; Gaitanis, G.; Katsanos, K.; Christodoulou, D.; Tsianos, E.; Bassukas, I. Psoriasis and inflammatory bowel disease: Links and risks. *Psoriasis* **2016**, *6*, 73–92, doi:10.2147/PTT.S85194.
- Morgan, K.; Boktor, M.; Ford, C.; Pham, L.; Morris, J.D.; Jordan, P.A.; Cvek, U.; Truttschl, M.; Alexander, J.S. Venous thromboembolism in IBD: Increased risk for women in CD? *Pathophysiology* **2019**, *26*, 163–168, doi:10.1016/j.pathophys.2019.03.001.
- Oldenburg, B.; Van Tuyl, B.A.C.; Van Der Griend, R.; Fijnheer, R.; Van Berge Henegouwen, G.P. Risk factors for thromboembolic complications in inflammatory bowel disease: The role of hyperhomocysteinaemia. *Dig. Dis. Sci.* **2005**, *50*, 235–240, doi:10.1007/s10620-005-1588-y.

17. Papa, A.; Danese, S.; Grillo, A.; Gasbarrini, G.; Gasbarrini, A. Review article: Inherited thrombophilia in inflammatory bowel disease. *Am. J. Gastroenterol.* **2003**, *98*, 1247–1251, doi:10.1111/j.1572-0241.2003.07491.x.
18. Antoni, L.; Nuding, S.; Wehkamp, J.; Stange, E.F. Intestinal barrier in inflammatory bowel disease. *World J. Gastroenterol.* **2014**, *20*, 1165–1179, doi:10.3748/wjg.v20.i5.1165.
19. Sochocka, M.; Donskow-Lysoniewska, K.; Diniz, B.S.; Kurpas, D.; Brzozowska, E.; Leszek, J. The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer's Disease—a Critical Review. *Mol. Neurobiol.* **2019**, *56*, 1841–1851, doi:10.1007/s12035-018-1188-4.
20. Zhang, B.; Wang, H.E.; Bai, Y.M.; Tsai, S.J.; Su, T.P.; Chen, T.J.; Wang, Y.P.; Chen, M.H. Inflammatory bowel disease is associated with higher dementia risk: A nationwide longitudinal study. *Gut* **2020**, *70*, 85–91, doi:10.1136/gutjnl-2020-320789.
21. Hatoum, O.A.; Binion, D.G. The vasculature and inflammatory bowel disease: Contribution to pathogenesis and clinical pathology. *Inflamm. Bowel Dis.* **2005**, *11*, 304–313, doi:10.1097/01.mib.0000160772.78951.61.
22. Schicho, R.; Marsche, G.; Storr, M. Cardiovascular complications in inflammatory bowel disease. *Curr. Drug Targets* **2015**, *16*, 181–188, doi:10.2174/1389450116666150202161500.
23. Singh, S.; Singh, H.; Loftus, E.V., Jr.; Pardi, D.S. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* **2014**, *12*, 382–393.e381, doi:10.1016/j.cgh.2013.08.023.
24. Brudek, T. Inflammatory Bowel Diseases and Parkinson's Disease. *J. Parkinsons Dis.* **2019**, *9*, S331–S344, doi:10.3233/JPD-191729.
25. Franke, A.; McGovern, D.P.B.; Barrett, J.C.; Wang, K.; Radford-Smith, G.L.; Ahmad, T.; Lees, C.W.; Balschun, T.; Lee, J.; Roberts, R.; et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat. Genet.* **2010**, *42*, 1118–1125, doi:10.1038/ng.717.
26. Lin, J.C.; Lin, C.S.; Hsu, C.W.; Lin, C.L.; Kao, C.H. Association between Parkinson's disease and inflammatory bowel disease: A nationwide Taiwanese retrospective cohort study. *Inflamm. Bowel Dis.* **2016**, *22*, 1049–1055, doi:10.1097/MIB.0000000000000735.
27. Villumsen, M.; Aznar, S.; Pakkenberg, B.; Jess, T.; Brudek, T. Inflammatory bowel disease increases the risk of Parkinson's disease: A Danish nationwide cohort study 1977–2014. *Gut* **2019**, *68*, 18–24, doi:10.1136/gutjnl-2017-315666.
28. Kosmidou, M.; Katsanos, A.H.; Katsanos, K.H.; Kyritsis, A.P.; Tsigvoulis, G.; Christodoulou, D.; Giannopoulos, S. Multiple sclerosis and inflammatory bowel diseases: A systematic review and meta-analysis. *J. Neurol.* **2017**, *264*, 254–259, doi:10.1007/s00415-016-8340-8.
29. Lin, C.H.; Kadakia, S.; Frieri, M. New insights into an autoimmune mechanism, pharmacological treatment and relationship between multiple sclerosis and inflammatory bowel disease. *Autoimmun. Rev.* **2014**, *13*, 114–116, doi:10.1016/j.autrev.2013.09.011.
30. Harper, J.W.; Zisman, T.L. Interaction of obesity and inflammatory bowel disease. *World J. Gastroenterol.* **2016**, *22*, 7868–7881, doi:10.3748/wjg.v22.i35.7868.
31. Jess, T.; Jensen, B.W.; Andersson, M.; Villumsen, M.; Allin, K.H. Inflammatory Bowel Diseases Increase Risk of Type 2 Diabetes in a Nationwide Cohort Study. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 881–888.e881, doi:10.1016/j.cgh.2019.07.052.
32. Corlateanu, A.; Mendez, Y.; Wang, Y.; Garnica, R.D.J.A.; Botnaru, V.; Siafakas, N. Chronic obstructive pulmonary disease and phenotypes: A state-of-the-art. *Pulmonology* **2020**, *26*, 95–100, doi:10.1016/j.pulmoe.2019.10.006.
33. Fricker, M.; Goggins, B.J.; Mateer, S.; Jones, B.; Kim, R.Y.; Gellatly, S.L.; Jarnicki, A.G.; Powell, N.; Oliver, B.G.; Radford-Smith, G.; et al. Chronic cigarette smoke exposure induces systemic hypoxia that drives intestinal dysfunction. *JCI Insight* **2018**, *3*, e94040, doi:10.1172/jci.insight.94040.
34. Ribaldone, D.G.; Pellicano, R.; Actis, G.C. The gut and the inflammatory bowel diseases inside-out: Extra-intestinal manifestations. *Minerva Gastroenterol. Dietol.* **2019**, *65*, 309–318, doi:10.23736/S1121-421X.19.02577-7.
35. Young, R.P.; Hopkins, R.J.; Marsland, B. The gut-liver-lung axis: Modulation of the innate immune response and its possible role in chronic obstructive pulmonary disease. *Am. J. Respir. Cell Mol. Biol.* **2016**, *54*, 161–169, doi:10.1165/rcmb.2015-0250PS.