Review

Macrophages in gut disease

Aris Alexiadis

Year 2, Medicine, University of Exeter
Email: aa598@exeter.ac.uk

What are macrophages?

Macrophages are innate (non-specific) immune cells that are the body's first line of defence.[1] Major organs in the body have their own native population of macrophages, deposited during embryonic development, including Kupffer cells (liver macrophages) and glial cells (brain macrophages).[2]

Macrophages in the gut

Recent insights have extended the characterisation of macrophage populations within the gut. Classically, macrophages can be activated to acquire one of two functional roles: M1 inflammation-causing macrophages and M2 anti-inflammatory macrophages. While M1 macrophages are in charge of attacking foreign bodies (such as disease-causing bacteria), M2 macrophages are responsible for wound healing.[3] Recent research shows macrophage function is less binary, with macrophage cells having a spectrum of different functions within the gut. For example, a transcriptomic study by Xue and colleagues, in Bonn, Germany, found that ten unique macrophage signatures were present, each occupying a different functional niche within the gut.[4] Imbalances in these macrophage populations in the gut have been thought to contribute to the underlying pathology of certain diseases, such as colorectal cancer and types of inflammatory bowel disease, such as ulcerative colitis (UC) and Crohn's disease.[5]

What makes macrophages in the gut different to others?

Macrophages in the gut have a unique transcription profile that can be dynamically influenced by molecular signals in their micro-environment.[6] Interestingly, saturated fats increase M1 polarisation of macrophages in the gut, and it is suggested that mice fed high-fat diets have a much larger M1 macrophage population in the gut when compared with lean mice, potentially leading to greater gut inflammation.[7] In addition to being one of the largest macrophage reservoirs in the body, the gastrointestinal (GI) tract is also one of the most microbe-rich organs, containing several trillion 'healthy' microbes, called the microbiome.[5] This environment is highly adaptive, being influenced by everything from diet to pathogens.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) refers to autoimmune dysfunction characterised by chronic inflammation of the colon and rectum. There are two major classifications of IBD: UC and Crohn's disease. In UC, the innermost lining of the large intestine is subject to inflammation and ulcers/sores.[8] Crohn's disease consists of inflamed patches that can occur anywhere within the intestinal tract, but commonly develop in the small intestine (**Figure 1**).[9]

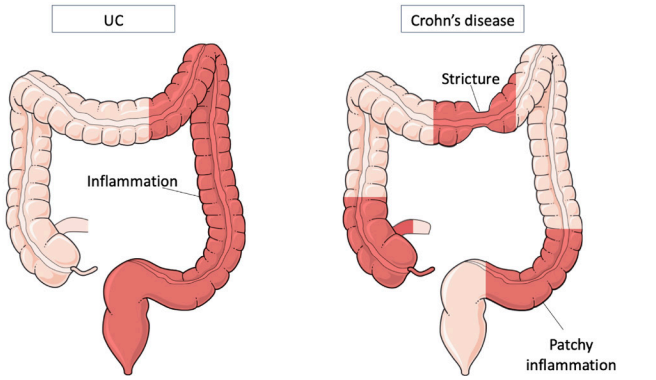

Figure 1. Summary of the pattern of disease in Crohn's disease and UC.[9]

Normally, M2 macrophages make up the majority of the gut macrophage population. However, a recent study found that the proportion of these macrophages decreases greatly in Crohn's disease, due to infiltration of M1 pro-inflammatory macrophages. Macrophages can be polarised from monocytes to the M1 or M2 state (**Figure 2**).

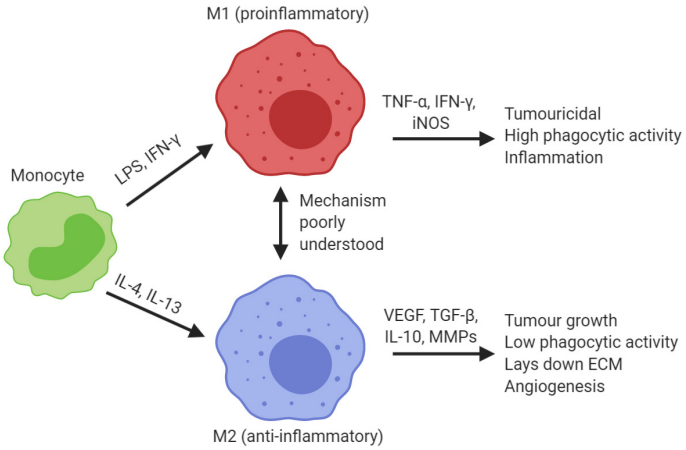

Figure 2. Binary polarisation model. M1 and M2 macrophages both derive from monocytes and their fate is decided by different stimuli. Due to their high plasticity, M1 macrophages can polarise into M2 macrophages and vice versa; however, the molecular mechanisms behind this are not well understood. M1 macrophages are pro-inflammatory and M2 macrophages are anti-inflammatory.[10] ECM, extracellular matrix; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; TGF-β, tumour growth factor-β; TNF-α, tumour necrosis factor-α; VEGF, vascular endothelial growth factor. Figure adapted from Hidalgo-Garcia et al,[11] distributed under the terms of the Creative Commons Attribution License (CC BY). Created with BioRender.com.

Treatment of Crohn's disease and UC depends on severity of the disease.[12] Treatment rationale is mainly based on targeting pro-inflammatory molecules, with surgery also being an option for patients, as stated in the National Institute for Health and Care Excellence (NICE) guidelines.[13,14] However, surgical intervention can bring about big declines in patient quality of life and may only provide temporary relief.

As previously stated, compounds in certain foods alter macrophage subtype populations in the gut. For example, genistein (a soya compound) was found to attenuate colitis through its induction of M2 macrophage polarisation.[15] Therefore, dietary modification could provide therapy for individuals with chronic gut disease. Additionally, it has been found that vitamin D supplementation decreases M1 macrophage-associated cytokine levels in IBD; however, it has not been found to induce M1 to M2 polarisation.[16] Use of therapeutic antibodies, such as infliximab, which targets the inflammatory mediator tumour necrosis factor α (TNFα), has proven to be controversial due to the unpredictable adverse response that patients with Crohn's disease have towards them. While most are probably influenced by multiple factors, it is thought that the patient's metabolism is the main determinant for lack of a beneficial response to anti-TNFα.[17]

Colorectal cancer

Colorectal cancer is the third most common cancer worldwide. Unlike IBD and its associated disorders, it is the polarisation of macrophages to M2 macrophages that contributes to colorectal cancer pathology. M2-like polarisation of tumour-associated macrophages (TAMs) seems to be linked to improved tumour blood flow through promoting expression of vascular endothelial growth factor, which initiates blood vessel formation.[18] TAMs also play an important role in tumour progression through inhibiting T cell anti-tumour responses. Most clinical investigations of macrophage subtypes in colorectal cancer have aimed to identify biomarkers that could aid clinicians in monitoring disease progression. In a recent study, levels of M2-like TAM were found to be correlated with distant tumour metastases through M2 TAM-driven release of circulating tumour cells. Monitoring these circulating tumour cells may help clinicians determine if post-operative chemotherapy is required. In addition, M2 macrophages seem to play a role in drug resistance in cancer therapy through expression of specific transporters (secreted protein acidic and cysteine rich [SPARC] and mannose receptor [MR]). This further highlights the diverse roles that gut macrophages can fulfil in different pathological states.[19]

Conclusions

Given the involvement of macrophages in chronic gut diseases, future research may benefit from developing therapeutics that alter macrophage behaviour in order to cure, or at least prevent exacerbation of chronic gut diseases. Regarding colorectal cancer, further research must be done and a description of standard M2 TAM levels and the establishment of reference ranges for clinicians must occur in order to enable the use of M2 TAM cells in diagnostic oncology as a predictive and/or prognostic biomarker.

References

1. Daisuke Hirayama, Tomoya Iida, Hiroshi Nakase. The phagocytic function of macrophage-enforcing innate immunity and tissue homeostasis. *Int J Mol Sci*, 2017; 19(1):92.
2. Gordon S, Plüddemann A. Tissue macrophages: heterogeneity and functions. *BMC Biol*, 2017; 15(1):53.
3. Schleier L, Wiendl M, Binder M-T, et al. Non-classical monocyte homing to the gut via α4β7 integrin is necessary for M2 macrophage-dependent intestinal wound healing. *Gastroenterology*, 2020; 69(2)252–263.
4. Xue J, Schmidt SV, Sander J, et al. Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity*, 2014; 40(2):274–88.
5. Isidro RA, Appleyard CB. Colonic macrophage polarization in homeostasis, inflammation, and cancer. *Am J Physiol-Gastrointest Liver Physiol*, 2016; 311(1):G59–G73.
6. Gerrick KY, Gerrick ER, Gupta A, et al. Transcriptional profiling identifies novel regulators of macrophage polarization. *PLoS One*, 2018; 13(12):e0208602.
7. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest*, 2007; 117(1):175–184.
8. Pei L, Ke Y, Zhao H, et al. Role of colonic microbiota in the pathogenesis of ulcerative colitis. *BMC Gastroenterol*, 2019; 19(1):10.
9. Steinbach EC, Plevy SE. The role of macrophages and dendritic cells in the initiation of inflammation in IBD. *Inflamm Bowel Dis*, 2014; 20(1):166–175.
10. Saqib U, Sarkar S, Suk K, et al. Phytochemicals as modulators of M1-M2 macrophages in inflammation. *Oncotarget*, 2018; 9(25):17937–17950.
11. Hidalgo-Garcia L, Galvez J, Rodriguez-Cabezas ME, et al. Can a conversation between mesenchymal stromal cells and macrophages solve the crisis in the inflamed intestine? *Front Pharmacol*, 2018; 9:179.
12. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol*, 2018; 53(3):305–353.
13. National Institute for Health and Care Excellence (NICE) (2013) Ulcerative colitis: management; 2013. Available from: www.nice.org.uk/guidance/NG130. Accessed: 27 September 2019.
14. National Institute for Health and Care Excellence (NICE) (2019) Crohn's disease: management. Available from: www.nice.org.uk/guidance/ng129. Accessed: 18 September 2019.
15. Abron JD, Singh NP, Price RL, et al. Genistein induces macrophage polarization and systemic cytokine to ameliorate experimental colitis. *PLoS One*, 2018; 13(7):e0199631.
16. Dionne S, Duchatelier C-F, Seidman EG. The influence of vitamin D on M1 and M2 macrophages in patients with Crohn's disease. *Innate Immun*, 2017; 23(6):557–565.
17. Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel diseases. *Inflamm Bowel Dis*, 2015; 21(7):1709–1718.
18. Des Guetz G, Uzzan B, Nicolas P, et al. Microvessel density and VEGF expression are prognostic factors in colorectal cancer. Meta-analysis of the literature. *Br J Cancer*, 2006; 94(12):1823–1832.
19. Zhao P, Yin W, Wu A, et al. Dual-targeting to cancer cells and M2 macrophages via biomimetic delivery of mannosylated albumin nanoparticles for drug-resistant cancer therapy. *Adv Funct Mater*, 2017; 27(44):1700403.