Janus-like monocytes regulate postoperative ileus

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In this issue of *Gut*, Farro *et al* and Pohl *et al* present new findings on the role of myeloid cells in postoperative ileus (POI).[1 2]

POI is a frequent consequence of abdominal surgery that can lead to costly delays in patient recovery.[3] The failure of peristalsis reflects paralysis of the smooth muscles of the intestine and several studies have suggested that this is dependent on macrophages in the muscularis externa (ME) layer of the gut wall that produce nitric oxide (NO).[4]

The intestine contains one of the largest pools of macrophages in the body, the majority of which is located in the lamina propria (LP) of the mucosa, near the epithelium. However macrophages are also present between the longitudinal and circular muscle layers of the ME, where they are in close proximity to the myenteric plexus.[5 6] Recent studies indicate that LP and ME macrophages are phenotypically and functionally distinct under steady-state conditions.[6] In particular, ME macrophages appear to have specialised tissue protection functions, including the production of factors such as bone morphogenic protein-2 (BMP2) that promote neuronal growth. In return, β_2-adrenergic receptors on ME macrophages allow them to be sustained by sympathetic neurons and these two-way interactions are at least partly dependent on the local microbiota.[6]

Mechanical insults such as abdominal surgery disrupt this steady-state balance, causing smooth muscle paralysis and infiltration of the small intestinal ME with blood-derived monocytes, mast cells and neutrophils. Studies in experimental animals have shown that POI is dependent on production of NO and other mediators by these myeloid cells and can be prevented by depleting cells of the monocyte-macrophage lineage in vivo.[4 7 8] Using mice with a selective defect in blood monocytes caused by deletion of the CCR2 chemokine receptor, Pohl *et al* and Farro *et al* now examine whether these effects are due to changes in the existing population of resident ME macrophages, or to the monocytes that have been recruited from the bloodstream.[1 2]These studies show that elicited monocytes are critical for producing NO and initiating POI in both the small intestine and colon, but there are important differences between these tissues in the mechanisms involved. First, resident ME macrophages can also contribute to POI in the small intestine, perhaps being activated directly by products of the local microbiota that have leaked through the mechanically damaged intestinal barrier.[1] This does not occur in the colon, where the authors suggest that resident macrophages have been rendered unresponsive by the larger load of microbiota in this site. The second difference is that POI in the small intestine is dependent on dendritic cells (DCs) that express both

CD103 and CD11b, a population that is unique to the intestine. These DCs produce interleukin 12 which stimulates T cells to make γ-interferon that then drives NO production by monocytes. Although monocytes in the colon also produce NO, $CD103^+CD11b^+$DCs are much less numerous here and it appears that the colonic monocytes may be stimulated directly by the local microbiota.[2]Understanding these anatomical differences has therapeutic implications, as the small intestine is the main target of POI and as the current papers show, interfering with elicited monocytes and resident macrophages requires different approaches.

Although both studies conclude that elicited monocytes are critical for the initiation of POI, Farro *et al* show that these cells have opposite effects during the resolution of POI, when they gradually acquire the features of tissue-protective macrophages.[1] Indeed this protective function may be the principal role of elicited monocytes in POI, as monocyte/macrophage depletion leads to enhanced pathology, increased neuronal damage and a delay in recovery. Although the authors suggest that some of the protective effects may be due to pre-existing resident macrophages, Janus-like behaviour of elicited monocytes of this kind has been shown recently in other models of inflammation, where they can give rise to mature, protective macrophages, or can themselves have anti-inflammatory roles.[9] For instance, production of prostaglandin E2 (PGE2) by monocytes prevents immunopathology in experimental intestinal toxoplasmosis by inhibiting the recruitment and activation of pathogenic neutrophils.[10] Neutrophils are a major component of the inflammatory infiltrate of POI and their numbers are sustained after depletion of monocytes. As they produce NO, reactive oxygen species and other potentially neurotoxic mediators, it seems quite possible that neutrophils may be the major player in the pathological features of POI. It would be interesting to explore the role of monocyte-derived PGE2 in recovery from POI.

Taken together, these studies suggest that targeting elicited monocytes could have therapeutic potential in modulating POI. Indeed, Farro *et al* show that administration of the monocyte-macrophage specific growth factor colony stimulating factor-1 (can promote resolution of experimental POI,[1] an approach that has also proved successful in preclinical studies of liver injury.[11] For this idea to be realised, it would clearly be important to confirm that the pathogenetic processes outlined in mice extend to humans, something that will require the development of suitable biomarkers that allow POI and monocyte recruitment to be monitored. At a more fundamental level, the reasons underlying the opposing effects of monocytes at different stages of POI need to be explored. For instance, do the reparative properties reflect the arrival of a new wave of monocytes that differ from those that are proinflammatory in the initiation phase and if so, do the different populations of monocytes show distinct phenotypical features or chemokine receptor requirements that might be exploitable for intervention? On the other hand, if the monocytes that arrive early in POI truly differentiate in situ and normally become protective, what drives this transition, is it defective in patients who suffer prolonged symptoms and can it be accelerated therapeutically? Although it is generally believed that elicited monocytes cannot give rise to long-lived resident macrophages in an inflammatory environment, this idea has recently been challenged[12] and in the case of a normally transient condition such as POI, permanent engraftment of reprogrammed monocytes may not be necessary. Finally, the mechanisms responsible for activating the DCs, monocytes and macrophages in POI remain to be determined. If a role for the microbiota and/or individual bacterial species can be identified, the prospect of

tailoring preoperative antibiotic use or even addition of probiotics might become a realistic option for preventing POI.

References

1. Farro G, et al. CCR2-dependent monocyte-derived macrophages resolve inflammation and restore gut motility in postoperative ileus. Gut 2017.
2. Pohl J-M, et al. Irf4-dependent CD103+ CD11b+ dendritic cells regulate monocyte and macrophage activation and intestinal peristalsis in postoperative ileus. Gut 2017.
3. Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. Am J Health Syst Pharm 2007;64:S3–S7.
4. Boeckxstaens GE, de Jonge WJ. Neuroimmune mechanisms in postoperative ileus. Gut 2009;58:1300–11.
5. Bain CC, Mowat AM. Macrophages in intestinal homeostasis and inflammation. Immunol Rev 2014;260:102–17.
6. Gabanyi I, Muller PA, Feighery L, et al. Neuro-immune interactions drive tissue programming in intestinal macrophages. Cell 2016;164:378–91.
7. Wehner S, Behrendt FF, Lyutenski BN, et al. Inhibition of macrophage function prevents intestinal inflammation and postoperative ileus in rodents. Gut 2007;56:176–85.
8. Engel DR, Koscielny A, Wehner S, et al. T helper type 1 memory cells disseminate postoperative ileus over the entire intestinal tract. Nat Med 2010;16:1407–13.
9. Rivera A, Siracusa MC, Yap GS, et al. Innate cell communication kick-starts pathogen-specific immunity. Nat Immunol 2016;17:356–63.
10. Grainger JR, Wohlfert EA, Fuss IJ, et al. Inflammatory monocytes regulate pathologic responses to commensals during acute gastrointestinal infection. Nat Med 2013;19:713–21.
11. Stutchfield BM, Antoine DJ, Mackinnon AC, et al. CSF1 restores innate immunity after liver injury in mice and serum levels indicate outcomes of patients with acute liver failure. Gastroenterology 2015;149:1896–909.
12. Gundra UM, Girgis NM, Gonzalez MA, et al. Vitamin A mediates conversion of monocyte-derived macrophages into tissue-resident macrophages during alternative activation. Nat Immunol 2017;18:642–53.