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EDITORIAL

Macrophages: The Missing Link in Diabetic Gastroparesis?

Gastroparesis is a clinical condition associated with delayed gastric emptying in the absence of mechanical obstruction. Patients present with nausea, vomiting, bloating, and early satiety. The underlying cause may be related to diabetes but also can be caused by upper gastrointestinal surgery, neurologic disease, collagen vascular disease, viral infections, and drugs.[1] In approximately 35% of patients there is no underlying cause. The pathogenesis and underlying cellular changes in diabetic gastroparesis are largely unknown. Changes in neurons, the interstitial cells of Cajal (ICC), and intestinal smooth muscle have been believed to have shown in diabetic gastroparesis. Macrophages have been believed to play some role in the development of diabetic gastroparesis but the mechanisms are not known.

In the article by Cipriani et al,[2] data are presented to support the role of macrophages in the development of delayed gastric emptying. Cipriani et al show the concept that macrophages are necessary for the pathogenesis of delayed gastric emptying. To do this, they used the *Csf1*$^{op/op}$ mice that lack biologically active macrophage-colony stimulating factor Csf1, resulting in the absence of Csf1-dependent tissue macrophages. Absence of macrophages in the muscle layer of the small intestine of these mice has been shown previously. Mice were injected with streptozotocin to make them diabetic and gastric emptying was assessed weekly. In addition, macrophages were identified by immunostaining and oxidative stress and messenger RNA levels were measured. The study showed that *Csf1*$^{op/op}$ mice have normal ICCs. When diabetes is induced there is increased oxidative stress in both the wild-type *Csf1*$^{+/+}$ mice and the *Csf1*$^{op/op}$ mice. Interestingly, despite this increased oxidative stress, the *Csf1*$^{op/op}$ mice did not develop loss of ICCs and the consequent delayed gastric emptying, however, the wild-type mice did. This led to the conclusion that the presence of muscle layer macrophages is required for the development of diabetic gastroparesis.

This work helps us to further understand the pathophysiology of diabetic gastroparesis with a focus on the muscle layer macrophages. It strengthens the role of ICC injury in diabetic gastroparesis and thereby highlights targets for the prevention and treatment of gastroparesis.

Macrophages present in the muscle layer can be polarized in response to changes in the microenvironment and are classified as M1 (proinflammatory macrophages) and M2 (anti-inflammatory macrophages). A previous study by Choi et al[3] showed that CD206-positive M2 macrophages are very important in preventing diabetic gastroparesis and this appears to be owing due to a heme oxygenase–dependent mechanism. Interestingly, in human beings, the number of CD206-positive M2 macrophages correlates with the number of ICCs, and this in turn correlates with gastric emptying.[4] In the *Csf1*$^{op/op}$ mice the baseline gastric emptying time was less that of the wild-type mice. It was noted that with the induction of diabetes in the *Csf1*$^{op/op}$ mice there was no reduction in gastric emptying. This was despite evidence for increased oxidative stress in these mice to the levels seen in the wild-type (WT) mice with delayed gastric emptying. The WT mice without delayed gastric emptying had lower oxidative stress levels, indicating that oxidative stress does play a role in diabetes-related delayed gastric emptying. The findings in this study suggest that the M1 macrophages may be releasing proinflammatory cytokines, which are required for the streptozotocin-induced damage to the ICCs noted in the wild-type but not *Csf1*$^{op/op}$ mice. This protection was seen despite the mice being equally hyperglycemic and having similar levels of oxidative stress. The lack of macrophages could protect against the loss of ICCs induced by streptozotocin. One point to be noted is that the *Csf1*$^{op/op}$ mice had developmental abnormalities including failure to develop teeth and some skeletal abnormalities. The investigators did ensure that the mice completed at least 50% of the meal to ensure comparable gastric emptying data between WT and *Csf1*$^{op/op}$ mice.

In summary, the study showed a role for macrophages in regulating the changes in the ICCs in diabetic gastroparesis, suggesting the role of M1 macrophages. Resident macrophages also could have a role in regulating gastrointestinal muscle contraction.[5] Future studies will need to examine the role of macrophages in other models of type 1 and type 2 diabetes. The current study advances the understanding of the complex pathophysiology of diabetic gastroparesis, focusing on the role of macrophages, and opens up a new area of research and potential therapeutic targets.

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Conflicts of interest
The author discloses no conflicts.

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