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Editorial

Is This the Era of Interstitial Cells of Cajal Transplantation?

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Article: Bone marrow derived Kit-positive cells colonize the gut but fail to restore pacemaker function in intestines lacking interstitial cells of Cajal
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Although not life-threatening, gastrointestinal (GI) motility disorders, such as achalasia, gastroparesis, intestinal pseudo-obstruction or slow transit constipation, can seriously affect a patient's quality of life.[1-5] Furthermore, since the pathophysiology of such disorders is often incompletely understood, development of a curative treatment is very difficult. Many studies have reported that loss of interstitial cells of Cajal (ICC), or injury to ICC networks can play an improtant role in various chronic GI motility disorders, including the aforementioned conditions.[6-10] ICC are known to control spontaneous contraction in GI smooth muscle through the generation of slow waves.[11-13] ICC also mediate inhibitory neurotransmission in such areas as the lower esophageal sphincter and the pylorus.[14] Therefore, loss of ICC or injury to ICC networks is strongly associated with the development of GI motility disorders. In this respect, recovery of lost ICC or disrupted networks may represent a revolutionary therapeutic modality for various GI motility disorders.

While it is known that ICC arise from mesenchymal precursors,[15] the regulation of their populations and life cycles has not been fully characterized. Although several animal studies have demonstrated the plasticity and regenerative capacity of ICC in neonatal and adult ICC-disruption models,[7,16,17] the exact underlying mechanisms are unclear. Among the several theories regarding ICC homeostasis, the role of stem cell is particularly prevalent.[18] In adults, pluripotent stem cells are derived from several organs, including the bone marrow (BM), adipose tissue and blood.[19] Recent studies have shown that BM-derived mesenchymal stem cells are not only capable of differentiating into osteoblasts, adipocytes, chondrocytes and myocytes, but also able to repopulate injured liver, lung or heart tissue following BM transplantation.[20] In the wake of these observations, the intriguing possibility that BM-derived stem cells could differentiate into ICC has been raised.

In this context, 2 recent studies have already generated positive results,[21,22] with 1 study even establishing evidence of improved motility.[22] In that study, however, detailed functional stud-

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ies to evaluate the functionality of incorporated ICC were not performed.

In this issue of *Journal of Neurogastroenterology and Motility*, the authors explored whether Kit$^+$ ICC networks, pacemaker activity and intestinal motility could be restored after transplantation of BM from control mice.[23] The author's group, comprising Prof. Kenton M Sanders, Prof. Sang Don Koh and Prof. Sean M Ward, among others, has a formidable track record of outstanding contributions to the field of ICC biology.[7,11,13-15,24,25] In 2013, the group published a report demonstrating the feasibility of ICC allotransplantation into the myenteric plexus of the small intestine. Allotransplantation of ICC into the intestines of W/W^V mutant mice (congenitally deficient in myenteric ICC; ICC-MY) successfully induced distinct Kit$^+$-ICC-MY networks and rhythmic pacemaker activity.[26] These results suggest that ICC allotransplantation of full-thickness muscle strips may represent a potential therapeutic option for patients with ICC-associated GI motility diseases. Currently, however, this method is not clinically feasible, owing to lack of clinical experience of its administration. BM transplantation, by contrast, is currently clinically available for treatments of such conditions as leukemia.

In this issue, the authors performed BM transplantations to W/W^V mutant mice through a similar method to that employed in clinical circumstance. And they tracked Kit$^+$ stem cells using Kit$^{+/copGFP}$ mice, whose Kit$^+$ cells express endogenous copGFP.

Transplantation successfully induced the BM-derived ICC clusters at the level of the myenteric plexus, consistent with two previous studies.[21,22] However, the range of ICC cluster distribution after BM transplantation was not concordant. Ishii et al[22] observed repopulation of ICC in the deep muscular plexus and submucosal plexus, as well as myenteric plexus following BM transplantation. While difference in the method of BM transplantation, or the interval between transplantation and experiment may have contributed to this discrepancy, further investigation under various conditions will be necessary to fully elucidate these diverging observations.

Despite successful repopulation, electrophysiological recordings using intracellular microelectrodes revealed an absence of muscular slow wave activity after transplantation, despite the degree and shape of the resting membrane potential being altered to resemble control conditions. Furthermore, spatio-temporal mapping of smooth muscle contractile activity revealed that normal activity could not be induced after transplantation. These observations also contradict the results published by Ishii et al,[22] which demonstrated increased gastric and intestinal transit.

However, it is not clear whether increased unitary potential but no slow wave observed in this study[23] is sufficient to accelerate intestinal transit observed in Ishii's study,[22] since electrophysiological study was not performed in Ishii's study.[22] Further study is required.

In summary, the authors conclude firstly, that BM-derived Kit$^+$ cells are capable of colonizing the intestinal myenteric plexus following BM transplantation, and secondary that despite successful colonization, they cannot develop into intact and functionally mature ICC under current conditions.

Clinically, BM transplantation still confers an extremely high risk of life-threatening complications. As such, even if recovery of lost or disrupted ICC networks were technically possible using this method, its adoption into widespread clinical practice would currently be unlikely. Nevertheless, this study may represent a significant first step towards a revolutionary curative treatment for debilitating GI motility disorders.

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