### KSL Cells Contribute to Vascular Stabilization in the Subacute Phase of SCI

In the present study, morphological vascular abnormalities, represented by an abnormally high number of vessels, many of which were enlarged, were observed at the epicenter of the injury site, which was devoid of astrocytes in the PBS group at day 14 after SCI. This abnormal pattern of vascular structures resembled abnormal vessels usually seen in tumors, CNS neurodegenerative diseases, or the injured brain, resulting in vascular hyperpermeability and blood–brain barrier dysfunction [26, 44, 45]. In the CNS, not only pericytes but also astrocytes are required for the formation of healthy blood vessels [45]. In contrast, the number and diameter of vessels in the spinal cord treated with KSL cells resembled the appearance of normal gray matter found in non-injured spinal cords. Angl is believed to play an important role not only in angiogenesis but also in vascular stabilization [46]. Ang-1 has also been shown to override VEGF-mediated effects on vascular permeability [47, 48]. In addition, overexpression of Angl stabilized tumor vessels and inhibited the growth of cancer [49, 50]. Therefore, we speculate that transplanted KSL cells contribute to vascular stabilization through Angl signaling and that Lnk deletion enhances these functions.

### KSL Cells Reduce Fibrous Scar Formation and Promote Axonal Regeneration

In this study, fibrous scar tissue in the injury site was immunostained with collagen type IV, which is a major structural component of basement membrane deposits of fibrous scars in the injured CNS [51]. At 6 weeks after SCI, the area of the collagen type IV$^{+}$ fibrous scar was reduced by the transplantation of KSL cells. In addition, these areas in the Lnk KO KSL group were smaller than those in the WT KSL group. On the basis of these data, we speculate that restricted infiltration of inflammatory cells caused by rapid migration of reactive astrocytes and vascular stabilization in the spinal cord treated with KSL cells might result in an overall reduction of the fibrous scar area.

On the other hand, axonal growth beyond the injury site was enhanced by the transplantation of KSL cells. In addition, Lnk deletion enhanced even further the function of KSL cells in promoting axon growth. Lesion scars are considered a major impediment for axon regeneration in the injured CNS [52]. In particular, fibrous scars are associated with axonal growth inhibitory molecules such as chondroitin sulfate proteoglycans, semaphorins, and ephrins [24, 38, 53, 54]. Therefore, a reduction in fibrous scar area might have been involved in the enhancement of the axonal growth observed in the present study. We could not detect long tract regeneration of either dopaminergic axons or serotonergic axons in this study. Recent studies have reported that regenerating local axons can form intraspinal neural circuits in the lesion site after SCI and make synaptic connections with descending-tract collaterals [55, 56]. The signal relay mechanism via short regenerated neuronal fibers might be responsible for the functional recovery seen in the present study.

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## Disclosure of Potential Conflicts of Interest

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