Authors' response by Kenji Kadomatsu
Department of Biochemistry, Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

On behalf of authors of J Neurosci 31: 17091-17102 (2011), I appreciate the valuable comments of Hilton et al. on this article. I think that the following comment in the Journal Club article is particularly important: "Conceivably, aggrecan-mediated neurite inhibition could require both CS and KS integrity, but with a variety of CSPGs and KSPGs present following SCI, further assessment of the relationship between the two glycosaminoglycans (GAGs) is warranted." We claimed in our article that all the components of proteoglycan, i.e., CS, KS and core protein, were essential for the proteoglycan-mediated inhibition of axonal regeneration/sprouting. According to our data, it is conceivable that an appropriate presentation of CS and KS on core protein is also important. To support this idea, we recently found that ADAMTS-4, a mammalian enzyme that digests core proteins of proteoglycans including aggrecan, brevican etc., ameliorates spinal cord injury (Tauchi et al., 2012). Based on our and others' data, many models could be postulated for the mechanism of action of CS and KS on axonal regeneration/sprouting. We eventually wish to verify these mechanisms.

To this end, we need to know the fine structures of the GAGs responsible for inhibiting neural plasticity after neuronal injury. If neurons have specific receptors for GAGs, these receptors may not recognize the whole, long GAG chains, but may recognize special structures (so-called functional domains), e.g., hyper-sulfation clusters, in GAGs. Importantly, these structures may change depending on the microenvironment. For example, 6-sulfated CS and disulfated KS are upregulated after spinal cord injury (Properzi et al., 2005; Imagama et al., 2011). The significance of GAG structure on neural plasticity has been demonstrated in a recent report on ocular dominance plasticity, which is usually seen only during the critical period in early childhood. This plasticity can be restored in adults in C6ST-1 transgenic mice that overexpress 6-sulafted CS (Miyata et al., 2012).

Elucidation of the functional domains in GAGs and their specific receptors will reveal the landscape in which GAGs regulate neural functions. Considering that GAGs are involved in many types of neural plasticity, including fear erasure and synapse plasticity involving lateral diffusion of AMPA receptors (Gogolla et al., 2009; Frischknecht et al., 2009), integration of glycobiology and neurobiology may greatly contribute to understanding neural activities.

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