Greene, J.D., Nystrom, L.E., Engell, A.D., Darley, J.M., and Cohen, J.D. (2004). Neuron *44*, 389–400.

Henrich, J., Boyd, R., Bowles, S., Camerer, C., Fehr, E., Gintis, H., and McElreath, R. (2001). Am. Econ. Rev. *91*, 73–78.

Kant, I. (1999). Metaphysical Elements of Justice (Indianapolis, IN: Hackett Publishing).

Knoch, D., Pascual-Leone, A., Meyer, K., Treyer, V., and Fehr, E. (2006). Science *314*, 829–832.

Poldrack, R.A. (2006). Trends Cogn. Sci. *10*, 59–63.

Sanfey, A.G., Rilling, J.K., Aronson, J.A., Nystrom, L.E., and Cohen, J.D. (2003). Science *300*, 1755–1758.

Spitzer, M., Fischbacher, U., Herrnberger, B., Gron, G., and Fehr, E. (2007). Neuron *56*, 185–196.

Thomson, J.J. (1976). Monist *59*, 204–217.

Whitman, J.Q. (2003). Buffalo Crimial Law Review *7*, 85–107.

PirB, a Second Receptor for the Myelin Inhibitors of Axonal Regeneration Nogo66, MAG, and OMgp: Implications for Regeneration In Vivo

Marie T. Filbin[1,*]
[1]Biology Department, Hunter College, 695 Park Avenue, New York, NY 10065, USA
*Correspondence: filbin@genectr.hunter.cuny.edu
DOI 10.1016/j.neuron.2008.12.001

Inhibitors of axonal regeneration in myelin are believed to be major contributors to the lack of regeneration in the adult CNS. Three of the four known myelin inhibitors, although very different structurally, interact with the same receptor, NgR. However, the absence of NgR has no effect on inhibition of neurite outgrowth in culture, and there is no improvement in CST regeneration in vivo. In a recent issue of *Science*, a second receptor for these myelin inhibitors was described, PirB, a receptor first described in the immune system. Will PirB be the answer to CST regeneration in vivo?

In the early 1990s, a monoclonal antibody, termed IN-1, was believed to be the solution to axonal regeneration in the adult mammalian spinal cord (Caroni and Schwab, 1988). At the time, the precise identity of the IN-1 antigen was unknown; however, it was known to be a component of the myelin membrane, thought to be one of the major obstacles to spontaneous axonal regeneration after injury. In culture the IN-1 antibody allowed neurons to extend long processes; when grown in the inhibitory environment of myelin and in vivo, it promoted axonal regeneration (Caroni and Schwab, 1988; Schnell and Schwab, 1990). The next steps, then, appeared simple—identify the IN-1 antigen and its receptor, and the molecular lock to promoting spinal axon regeneration would be opened.

Alas, as with most biological problems, the answer was not so simple. Even before the IN-1 antigen had been cloned, another potent regeneration inhibitor was identified in myelin, the myelin-associated glycoprotein (MAG) (McKerracher et al., 1994; Mukhopadhyay et al., 1994). The subsequent identification of the IN-1 antigen (which may be one of many, but the only one identified to date) as a protein termed NogoA, revealed that the protein carried two inhibitory domains, only one of which, within the amino terminus, termed Amino-Nogo, was recognized by the IN-1 antibody; the second inhibitory domain, carried by a string of 66 amino acids, was termed Nogo66 (GrandPre et al., 2000; Huber and Schwab, 2000; Prinjha et al., 2000). Later, a third myelin protein, the oligodendrocyte-myelin glycoprotein (OMgp) was also shown to be inhibitory for neurite outgrowth (Wang et al., 2002). So now there were four inhibitors (two on NogoA) identified in myelin. As these inhibitors shared no sequence or even domain similarity with each other, it was presumed they would each have their own receptor. It came as a real surprise, then, that the binding partner identified for Nogo66, termed Nogo receptor (NgR), was also shown to bind MAG and OMgp (Domeniconi et al., 2002; Fournier et al., 2001; Wang et al., 2002). So, again, a somewhat simple answer to axonal regeneration in vivo presented itself; namely, if this single receptor could be neutralized or eliminated in vivo, then the effects of three of the four major inhibitors in myelin would be lost, and regeneration should proceed.

Not so. Two groups reported studies in which NgR had been knocked out. One study, from the Strittmatter group, reported a loss of the growth cone collapse response to the myelin inhibitors and limited regeneration of the raphespinal and rubrospinal tracts, but no regeneration of the corticospinal tract (CST) (Kim et al., 2004; Zheng et al., 2005). A second study, by the Tessier-Lavigne group,

reported no difference in inhibition of neurite outgrowth by myelin inhibitors of neurons from NgR null mice and wild-type mice, and again no regeneration of the CST (Zheng et al., 2005). The observation that neurons from the NgR null mice were still inhibited by Nogo66 strongly suggested that there was another receptor, at least for Nogo66. In a recent paper published in *Science*, a second receptor, which bound not only Nogo66 but also MAG and OMgp and which was capable of exerting inhibition of neurite outgrowth, was described (Atwal et al., 2008). The receptor, first described on cells of the immune system, and more recently shown to be also in the nervous system (Syken et al., 2006), is paired immunoglobulin-like receptor B (PirB).

Based on their results with the NgR null mice (Zheng et al., 2005), in their quest for a second Nogo66 receptor, the Tessier-Lavigne group screened a human cDNA expression library for Nogo66 binding partners. They identified two such partners—again, NgR and human leukocyte immunoglobulin (Ig)-like receptor B2 (LILRB2), which, in humans, is one of five highly homologous family members of B-type LILR, which contain six Ig-like domains in their extracellular segments. There is only one mouse ortholog of human LILRB2, PirB, and although it contains four rather than six Ig-like domains and bears only 50% homology with the human, PirB binds not only Nogo66 but also MAG and OMgp, with, at least for MAG, the same affinity as binding to the NgR. To demonstrate that there was some functional relevance to this binding, the authors generated a high-affinity monoclonal antibody to PirB. They showed that this PirB antibody was able to partially block the inhibition by Nogo66 and total myelin of cerebellar neurons, as well as inhibition by all three inhibitors for dorsal root ganglion neurons. Similar effects on partial block of inhibition were observed when neurons from a PirB mutant mouse were used. To assess if blocking both PirB and NgR resulted in a greater block of inhibition, neurons from NgR null mice were used together with the PirB blocking antibody. As they reported previously (Zheng et al., 2005), cerebellar neurons from the NgR null mouse were inhibited as effectively by Nogo66 as cerebellar neurons from wild-type mice. They now also showed that for NgR null neurons the PirB antibody partially, but only partially, blocked inhibition by Nogo66, strongly suggesting that there is yet another Nogo66 receptor. Curiously, the same combination—NgR null cerebellar neurons and PirB antibody—was able to completely overcome inhibition by total myelin. This implies either that interaction of Nogo66 with its putative third receptor plays no role in inhibition by total myelin, as this interaction should be unaffected by the PirB antibody and by the absence of the NgR, or that Nogo66 plays little or no role in inhibition of neurite outgrowth from cerebellar neurons by total myelin—a conclusion difficult to reconcile with the strong inhibition by Nogo66 when presented to cerebellar neurons alone and its reported abundance in myelin (GrandPre et al., 2000). It would have been interesting to see these combination NgR null/PirB antibody experiments carried out with MAG and OMgp alone. Would the results be like those with Nogo66 or would their inhibition be blocked completely when NgR and PirB are blocked? The latter outcome would be the prediction from the studies with total myelin, but if the former was the outcome, then it raises the question of whether inhibition by purified myelin is truly the sum of the individual inhibitors. However, from the studies described in Atwal et al. (2008), the NgR and PirB receptors appear to be responsible for transducing all the inhibitory signals exerted by total myelin.

What is particularly interesting is that it was previously reported that in the PirB mutants the critical period during which experience-driven plasticity of ocular dominance can occur during development is extended (Syken et al., 2006), and a similar effect had also been reported in NgR null mice (McGee et al., 2005). In the study with the NgR null mice, a clear correlation with the progress of myelination and closure of the critical period in wild-type mice was described. From the time when myelin was first described as being inhibitory for process outgrowth, the question has been why this alternative function for this insulating membrane evolved. Is there a developmental, physiological relevance to having inhibitors of axonal growth in myelin? Now, with two studies demonstrating extension of the critical period in the absence of either myelin-inhibitor receptor, the answer seems to be yes. Inhibitors in myelin, acting through either NgR or PirB, terminate plasticity, most likely by limiting sprouting. The question remains, however, why the absence of either NgR or PirB is sufficient to extend the critical period but both must be blocked to overcome inhibition by myelin in culture.

The identification of PirB as another receptor for three major myelin inhibitors of regeneration expands our understanding but adds to the complexity of what prevents axonal regeneration after injury to the brain and spinal cord. This in turn adds PirB to the possible targets for therapeutic intervention to promote regeneration in vivo. There are, of course, many questions still to be answered—for example, is PirB part of a receptor complex, or does it act alone? How does it signal, and does the signaling converge on the Rho pathway known to be activated via NgR signaling? Does myelination terminate other forms of developmental plasticity? The biggest question of all, however, is whether extensive regeneration of the CST will occur in a NgR-PirB double knockout—the holy grail for axonal regeneration in vivo.

REFERENCES

Atwal, J.K., Pinkston-Gosse, J., Syken, J., Stawicki, S., Wu, Y., Shatz, C., and Tessier-Lavigne, M. (2008). Science *322*, 967–970.

Caroni, P., and Schwab, M.E. (1988). Neuron *1*, 85–96.

Domeniconi, M., Cao, Z., Spencer, T., Sivasankaran, R., Wang, R.C., Nikulina, E., Kimura, N., Cai, H., Deng, K., Gao, Y., He, Z., and Filbin, M.T. (2002). Neuron *35*, 283–290.

Fournier, A.E., GrandPre, T., and Strittmatter, S.M. (2001). Nature *409*, 341–346.

GrandPre, T., Nakamura, F., Vartanian, T., and Strittmatter, S.M. (2000). Nature *403*, 439–444.

Huber, A.B., and Schwab, M.E. (2000). Biol. Chem. *381*, 407–419.

Kim, J.E., Liu, B.P., Park, J.H., and Strittmatter, S.M. (2004). Neuron *44*, 439–451.

McGee, A.W., Yang, Y., Fischer, Q.S., Daw, N.W., and Strittmatter, S.M. (2005). Science *309*, 2222–2226.

McKerracher, L., David, S., Jackson, D.L., Kottis, V., Dunn, R.J., and Braun, P.E. (1994). Neuron *13*, 805–811.

Mukhopadhyay, G., Doherty, P., Walsh, F.S., Crocker, P.R., and Filbin, M.T. (1994). Neuron *13*, 757–767.

Prinjha, R., Moore, S.E., Vinson, M., Blake, S., Morrow, R., Christie, G., Michalovich, D., Simmons, D.L., and Walsh, F.S. (2000). Nature *403*, 383–384.

Schnell, L., and Schwab, M.E. (1990). Nature *343*, 269–272.

Syken, J., Grandpre, T., Kanold, P.O., and Shatz, C.J. (2006). Science *313*, 1795–1800.

Wang, K.C., Koprivica, V., Kim, J.A., Sivasankaran, R., Guo, Y., Neve, R.L., and He, Z. (2002). Nature *417*, 941–944.

Zheng, B., Atwal, J., Ho, C., Case, L., He, X.L., Garcia, K.C., Steward, O., and Tessier-Lavigne, M. (2005). Proc. Natl. Acad. Sci. USA *102*, 1205–1210.