magnetic properties must be found that can be processed next to metal layers at relatively low temperatures (<900°C), with little or no chemical interaction that would degrade properties.

The technical problems presented by microwave materials pose rich scientific challenges to the materials science community. Depending on the operating frequency and application—base station infrastructure or handheld device—materials with a wide range of dielectric and magnetic properties are needed, all with improved performance at lower cost. As engineers develop new concepts and designs for tomorrow's communication systems, they will be relying on progress in understanding and controlling these materials.

References and Notes

1. W. R. Snyder, C. L. Bragaw, *Achievement in Radio* (NBS Spec. Pub. 555, U.S. Government Printing Office, Washington, DC, October 1986).
2. R. D. Richtmyer, *J. Appl. Phys.* **10**, 391 (1939).
3. H. M. O'Bryan, J. Thomson, J. K. Plourde, *J. Am. Ceram. Soc.* **57**, 450 (1974).
4. T. Negas *et al.*, *Am. Ceram. Soc. Bull.* **72**, 80 (1993).
5. R. J. Cava, *J. Mater. Chem.* **11**, 54 (2001).
6. T. Negas, G. Yeager, S. Bell, R. Amren, in *Chemistry of Electronic Materials* (NIST Spec. Pub. 804, U.S. Government Printing Office, Washington, DC, 1991), pp. 21–37.
7. P. K. Davies, in *Materials and Processes for Wireless Communications*, T. Negas, H. Ling, Eds., vol. 53 of *Ceramic Transactions* (American Ceramic Society, Westerville, OH, 1995), pp. 137–151, 179–196.
8. S. Penn, N. Alford, in *Handbook of Low and High Dielectric Constant Materials and Their Applications, Vol. 2*, H. S. Nalwa, Ed. (Academic Press, New York, 1999), chap. 10.
9. I. M. Reaney, E. L. Colla, N. Setter, *Jpn. J. Appl. Phys.* **33**, 3984 (1994).
10. I. M. Reaney *et al.*, *Phil. Mag.* **81**, 501 (2001).
11. R. Christofferson, P. K. Davies, X. Wei, T. Negas, *J. Am. Ceram. Soc.* **77**, 1441 (1994).
12. P. K. Davies, J. Tong, T. Negas, *J. Am. Ceram. Soc.* **80**, 1727 (1997).
13. I. Levin *et al.*, *J. Solid State Chem.* **156**, 122 (2001).
14. E. Cockayne, B. P. Burton, *Phys. Rev. B* **62**, 3735 (2000).
15. V. Zelezny *et al.*, *Phys. Rev. B*, in press; preprint: Eric.Cockayne@nist.gov.
16. S. Kamba *et al.*, *J. Appl. Phys.* **89**, 3900 (2001).
17. R. Zurmuehlen *et al.*, *J. Appl. Phys.* **77**, 5351 (1995).
18. The identification of a commercial firm does not imply endorsement or recommendation by the National Institute of Standards and Technology.
19. T. Negas, personal communication.
20. York, UK, 1 to 3 September 2002 (see www2.umist.ac.uk/material/research/microwave/meetings/MMA2002/Default.htm). The meeting was organized by the Microwave Dielectrics Network (www.umist.ac.uk/microwave).
21. J. Pendry, *Phys. World* **14**, 47 (September 2001).
22. W. J. Chappell, M. P. Little, L. P. B. Katehi, *IEEE Micro. Wire. Comp. Lett.* **11**, 246 (2001).

PERSPECTIVES: NEUROBIOLOGY

A Glial Spin on Neurotrophins

Barbara L. Hempstead and James L. Salzer

The membranous myelin sheath that surrounds the axons of neurons enables the efficient and rapid propagation of action potentials, which is essential for the smooth operation of the vertebrate nervous system. The myelin sheath is produced by nonneuronal glial cells: Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS). During development, glial cells and neurons depend on each other for survival and differentiation. Among the most dramatic but least understood of these cell-cell interactions are those initiating the formation of myelin. Myelination involves striking changes in the differentiation and morphology of glial cells (see the figure). In addition, axons regulate the myelination program of glia during development through a combination of positive and negative signals (*1*). These still-mysterious signals ensure that myelination is restricted to specific types of axons and is switched on at the appropriate time. On page 1245 of this issue, Cosgaya *et al.* (*2*) report that nerve growth factors called neurotrophins are emerging as both positive and negative modulators of myelination. In particular, they show that the p75 neurotrophin receptor positively regulates myelination by Schwann cells in the PNS.

In earlier work, Cosgaya and colleagues described the opposing effects of neurotrophins on myelination (*3*). They showed that addition of brain-derived neurotrophic factor (BDNF) to cocultures of Schwann cells and neurons, or injecting BDNF next to the developing sciatic nerve promoted myelination; in contrast, neurotrophin-3 (NT3) inhibited myelination in both sets of experiments. Interestingly, BDNF, but not NT3, persisted at significant levels in the cocultures through the onset of myelination, suggesting that this neurotrophin serves as a promyelinating signal. These findings are strikingly similar to those of another study showing that BDNF is a paracrine signal that promotes the differentiation of avian Schwann cells cocultured with neurons, and that NT3 is inhibitory (*4*). This study also revealed that neurons, rather than glial cells, are the major source of BDNF (*4*).

Neurotrophins mediate their effects by binding to two classes of receptor: the Trk receptor tyrosine kinases and the p75 receptor, a member of the tumor necrosis factor receptor superfamily that binds to all neurotrophins. Nerve growth factor (NGF), BDNF, and NT3 bind selectively to TrkA, TrkB, and TrkC receptors, respectively; truncated forms of each of these Trk receptors also exist (*5*). Both Schwann cells and neurons express neurotrophin receptors, and so neurotrophins may act on glial cells either directly or indirectly (through modulation of the myelination signals from axons). The neurons used in the Cosgaya *et al.* study (*2*) were dependent on NGF for their survival but not on BDNF or NT3, suggesting that BDNF and NT3 regulate myelination through direct effects on Schwann cells.

Schwann cells express p75 during development, prior to myelination, as well as kinase-active TrkC and kinase-inactive, truncated isoforms of TrkB and TrkC (*6*). Cosgaya *et al.* now demonstrate that p75 mediates the myelin-promoting effect of BDNF and that kinase-active TrkC transduces the myelin-inhibitory effect of NT3 (*2*). Thus, antibodies to p75, but not antibodies to TrkB, blocked the myelin-promoting effect of BDNF; pharmacological inhibition of Trk kinase activity blocked the ability of NT3 to inhibit myelination. Peripheral nerves of mice deficient in p75 are hypomyelinated and, as Cosgaya *et al.* show (*2*), are unresponsive to the myelin-promoting effects of BDNF. Because p75 is rapidly down-regulated at the onset of myelination (*1*), p75 is likely to promote the initial axon-glial interactions that precede, and are required for, myelination rather than myelination itself (see the figure). Among these early events are Schwann cell migration along and initial ensheathment of axons, both of which are impaired in p75-deficient mice (*7*). These findings also imply that p75-dependent effects reflect the activity of the p75 receptor expressed by Schwann cells and not that expressed by axons. However, to distinguish between these two possibilities, it will be necessary to analyze nerves from mice lacking p75 only in Schwann cells, or to culture Schwann cells from p75-deficient mice with wild-type neurons.

What downstream signaling molecules might distinguish the myelin-promoting effects of BDNF-induced p75 activation from the myelin-inhibitory effects of NT3-induced TrkC activation? Because p75 and Trk receptors use many unique intracellular signaling pathways (*5*, *8*), Schwann cells may interpret the effects of local neurotrophin ligands through differential receptor binding and activation. The pathways downstream of the Trk receptors are well characterized, and further analysis should provide new insights into the negative regulation of myelination (*5*). Elucidating how activation of p75 promotes myeli-

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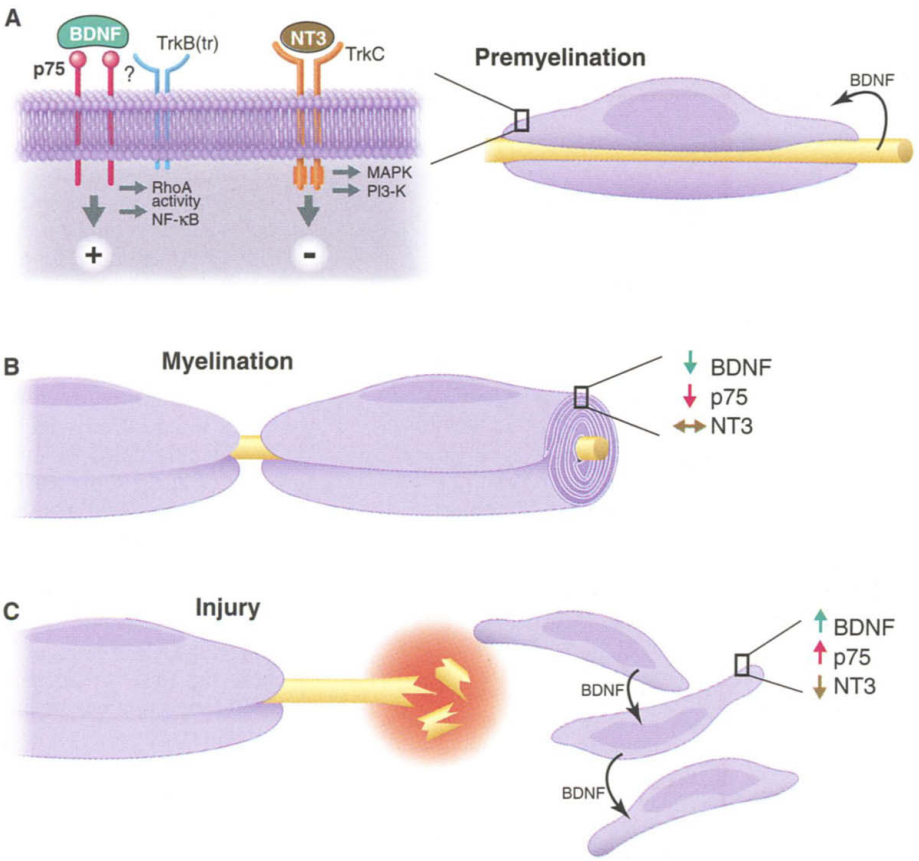
nation will be more challenging. In their new work, Cosgaya *et al.* demonstrate that binding of BDNF to p75 induces myelination, whereas NT3 and NGF (which bind to p75 with equivalent affinity) have no effect. How might p75 differentiate between these highly related ligands to mediate distinct biological outcomes? Binding of different neurotrophins to p75 could potentially induce unique conformational changes in p75, leading to differential signaling. Alternatively, BDNF may activate receptor complexes composed of p75 and truncated TrkB receptors. Such complexes could induce signaling cascades that are distinct from those induced by clustering of p75 receptors alone via NT3 or NGF (*8*). Distinct biological actions of p75 in a complex with a truncated Trk receptor have been suggested by studies of neocortical subplate neurons and neural crest cells. Further investigations to delineate the downstream effectors of p75 should help to elucidate the signaling events associated with myelination, which are poorly understood. One candidate is the transcription factor NF-κB, which is an important regulator of Schwann cell myelination and can be activated by binding of ligand to p75 (*9*). The p75 receptor has also been implicated in control of RhoA activity and assembly of the actin cytoskeleton (*10*).

The neurotrophins are likely to modulate myelination in both the PNS and CNS, although they do not appear to be essential. Thus, the effects of BDNF on myelination are most pronounced with short-term treatment and over time become less striking (*2*). In addition, although most BDNF-deficient mice die perinatally, myelin appears to form normally in the PNS of the occasional animal that survives for several weeks (*11*). Interestingly, BDNF-deficient mice exhibit marked hypomyelination in the CNS, findings originally interpreted as secondary to a reduction in the size of CNS axons (*11*). In light of the new work, it is possible that BDNF directly affects oligodendrocytes in the CNS as they also express both p75 and truncated Trk receptors. That both BDNF and NT3 promote myelination by oligodendrocytes is suggested by their combined effects on oligodendrocyte-neuron cocultures (*12*) and in experimental models of spinal cord injury (*13*).

In addition to its importance during development, p75 is likely to be a primary player in the repair of nerve injury because it is rapidly up-regulated in Schwann cells following axon transection (*6*). The functional significance of this injury response has long been obscure. The findings of Cosgaya *et al.* (*2*) suggest that reexpression of p75 by Schwann cells after injury could promote remyelination of regenerating nerve fibers. Consistent with this, BDNF increases after injury but NT3 decreases (*6*). Recent studies also demonstrate that supplementary BDNF enhances remyelination of regenerating nerve fibers (*14*).

Following injury, the p75 receptor may have a second job: to promote the programmed cell death of Schwann cells deprived of neuronal trophic support (*15*). There is a similar induction of p75 expression in oligodendrocytes following spinal cord injury, together with an increase in a newly described ligand for p75, the precursor form of NGF (pro-NGF) (*16*). Pro-NGF selectively binds to and activates p75, but not Trk receptors (*17*). It also effectively induces apoptosis of oligodendrocytes that express p75 (*16*). Further analysis of the cell-specific and temporal induction of neurotrophin isoforms, and their receptors, will be needed to clarify their role in the injury response in both the PNS and CNS. Inducible and cell-specific gene targeting will be useful strategies to distinguish between axonal and glial effects of neurotrophin-modulated survival and differentiation.

The new work extends the list of remarkably diverse tasks that neurotrophins and their receptors carry out during development. Neurotrophins now may be viewed more correctly as paracrine signals that mediate bidirectional signaling between neurons and the glia that ensheath them, rather than as factors that act on neurons alone. The new findings are likely to prompt a reexamination of the pathology of mice in which neurotrophins and their receptors have been ablated, and may provide new therapeutic opportunities for treating myelin and peripheral nerve disorders.



All wrapped up. (**A**) Neurotrophin receptors and signaling. The p75 receptor, either alone or in conjunction with a truncated TrkB receptor, is expressed in the Schwann cell membrane. Here, p75 transduces a promyelinating signal from the neurotrophin BDNF, or regulates survival of Schwann cells. TrkC receptors, which specifically bind to NT3, inhibit myelination via signaling pathways dependent on kinase activation. Just before the onset of myelination during development, NT3 levels diminish, thus relieving the block on myelination. BDNF persists and promotes myelination by binding to the p75 receptors expressed by Schwann cells. BDNF is likely to be released by neurons, although Schwann cells are a potential additional source. (**B**) In the mature nerve, p75 continues to be expressed by nonmyelinating Schwann cells but not by myelinating Schwann cells; both BDNF and NT3 levels decrease, and Trk receptors are minimally expressed. (**C**) After nerve injury, the axons and myelin sheaths of neurons degenerate. There is a dramatic increase in the expression of p75 by Schwann cells in the distal stump but a minimal change in the expression of Trk receptors. Schwann cells increase their expression of BDNF and decrease their expression of NT3 (which may be autocrine signals regulating Schwann cell survival and differentiation).

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References

1. R. Mirsky, K. R. Jessen, *Brain Pathol.* **9**, 293 (1999).
2. J. M. Cosgaya, J. R. Chan, E. M. Shooter, *Science* **298**, 1245 (2002).
3. J. R. Chan, J. M. Cosgaya, Y. J. Wu, E. M. Shooter, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 14661 (2001).
4. M. Pruginin-Bluger, D. L. Shelton, C. Kalcheim, *Mech. Dev.* **61**, 99 (1997).
5. E. J. Huang, L. F. Reichardt, *Annu. Rev. Neurosci.* **24**, 677 (2001).
6. S. S. Scherer, J. L. Salzer, in *Glial Cell Development*, K. R. Jessen, W. D. Richardson, Eds. (Oxford Univ. Press, London, 2001), pp. 299–330.
7. C. A. Bentley, K. F. Lee, *J. Neurosci.* **20**, 7706 (2000).
8. B. L. Hempstead, *Curr. Opin. Neurobiol.* **12**, 260 (2002).
9. J. C. Nickols *et al.*, *Society for Neuroscience Abstr.* **819**, 15 (2002).
10. T. Yamashita, K. L. Tucker, Y. A. Barde, *Neuron* **24**, 585 (1999).
11. A. Cellerino, P. Carroll, H. Thoenen, Y. A. Barde, *Mol. Cell. Neurosci.* **9**, 397 (1997).
12. H. Yan, P. M. Wood, *J. Neurosci. Res.* **62**, 329 (2000).
13. D. M. McTigue, P. J. Horner, B. T. Stokes, F. H. Gage, *J. Neurosci.* **18**, 5354 (1998).
14. J. Y. Zhang *et al.*, *Eur. J. Neurosci.* **12**, 4171 (2000).
15. D. E. Syroid *et al.*, *J. Neurosci.* **20**, 5741 (2000).
16. M. S. Beattie *et al.*, *Neuron* **36**, 375 (2002)
17. R. Lee, P. Kermani, K. K. Teng, B. L. Hempstead, *Science* **294**, 1945 (2001).

PERSPECTIVES: PALEOCLIMATE

A Poisoned Chalice?

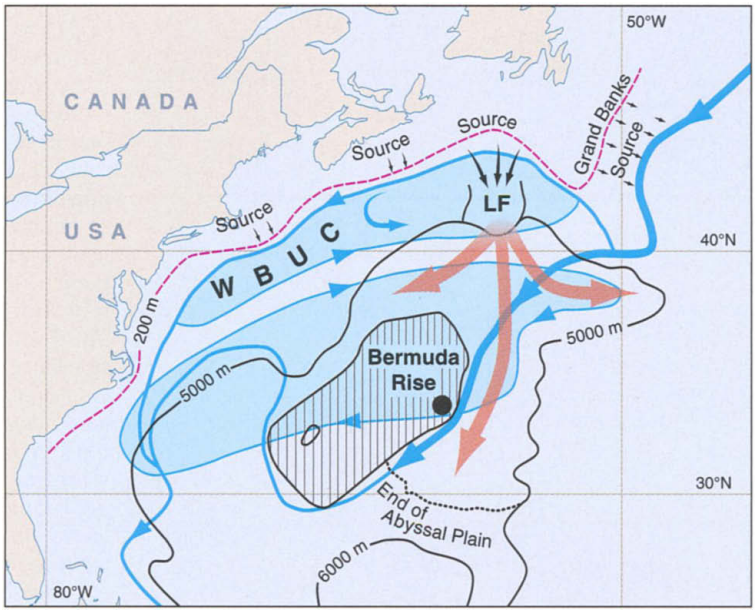
I. Nick McCave

Like King Arthur's knights searching for the Holy Grail, marine geologists search for areas with high sedimentation rates, because only cores drilled in these areas can provide high-resolution records of past climate. But on page 1224 of this issue, Ohkouchi *et al.* (*1*) show that this Grail may be a poisoned chalice.

High sedimentation rates—ideally, 50 to 100 cm per 1000 years—are necessary for high resolution because most marine sediments are mixed by bottom-dwelling organisms on a scale of a few centimeters. In the North Atlantic, average rates are about 2 to 4 cm per 1000 years away from continental margins (*2*), and about 10 cm per 1000 years on continental margins. In the North Pacific, they are even lower (less than 1 cm per 1000 years). High sedimentation rates are thus anomalous. The question is whether cores with anomalous rates of deposition are also anomalous in other ways—for example, in the climatic signals they contain.

Of course, one person's anomaly is another's signal. Whether a core is interpreted correctly depends on which assumptions are made with regard to the sedimentation process. We can envisage three main scenarios for sediment deposition.

First, material sinking to the seafloor may consist entirely of material from the upper ocean, comprising both biological material and wind-blown dust. In such a pelagic (upper ocean) setting, the material is presumed to be static once it has landed on the seafloor. It is a mixture of sand-sized (>63 μm diameter) components, mainly shells of foraminifera, and fine particles (<63 μm diameter), mainly dust and the detritus of phytoplankton. The fine particles form aggregates and sink rapidly to the seafloor, where they fall apart. This scenario applies to most of the deep ocean (away from continental boundaries), where bottom sediments reflect the material leaving the upper ocean and its processes and properties. However, sedimentation rates are extremely low, so this is not where Grail hunters go.



Sediment transport at Bermuda rise. The fine plumes of turbidity currents (gray) from the Laurentian fan (LF) are entrained by deep-ocean flows (blue lines) and trapped in regions of recirculation (pale blue areas) (*14*). Material eroded by storms from the eastern Grand Banks may be carried to Bermuda Rise by the North Atlantic Deep Water (NADW) (thick blue arrow). Resuspension from the upper continental margin of Nova Scotia and the northern United States feeds into the recirculating gyre and may find its way to Bermuda Rise, especially when sea levels are low during glacial periods. The core of Ohkouchi *et al.* (*1*) (black spot) lies under the NADW, in the recirculation and near the turbidity current flow path. WBUC, Western Boundary Undercurrent.

Second, the thickness of the sediments bearing pelagic signals may be increased by laterally transported material that does not carry a temperature or other signal of interest. In areas where current-controlled rapid deposition creates sediment drifts, foraminifera are quickly buried and hence relatively immobile, providing good time markers. This scenario is envisaged, neglecting the likely mobility of the fine particles, when records are interpreted as though they were pelagic, with high resolution conferred by added sediment. The laterally transported material comprises clay (<2 μm diameter) and silt (2 to 63 μm diameter) carried in suspension.

The third scenario is the same as the second, but focuses attention on the properties of the laterally supplied silt and clay. These fine materials may carry information on their source or on how vigorous the bottom flow is. The pelagic input then provides material on which to base stratigraphy and inference of age. (Reprehensibly, many paleoceanographers simply throw the fine material away!) In most sediment drifts, the third scenario is correct—the lateral input is not signal-free—nevertheless, the first two scenarios are often assumed for interpretation (*3*).

Ohkouchi *et al.* (*1*) demonstrate elegantly the interpretative pitfall in assuming the second scenario when the third applies. They show that at the same level in their sediment core from Bermuda Rise, the radiocarbon ages of unsaturated alkenones [fine-grained organic compounds synthesized by plankton in the upper ocean from which estimates of sea surface temperature (SST) are obtained] greatly exceed those of foraminifera (*1*).

Keigwin has argued that the foraminifera at this location show SST changes associated with the Little Ice Age (late 15th to late 19th century AD) (*4*). If the first or second

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