human barrier, it would now be very useful to know quickly whether a similar event may occur for the prion strains of deer and elk affected by the prion diseases called chronic wasting disease (CWD), which is endemic in parts of the United States. The answer to this question is of obvious relevance to public health. Another question is the role of the glycans linked to PrP^{Sc} in prion strain diversity and species barrier, an issue beyond the scope of the study by Peretz et al. Recently, it has been shown that two distinct human prion "strains" with the same amino acid sequence differ markedly in the type and amount of their glycans (Pan et al. 2001). Could the presence of different glycans explain the distinct conformation of prion strains that have the same primary structure?

Several assays that can identify conformational properties of PrP^{Sc} are currently available. The first assay that pointed to a relation between prion strain diversity and structure is based on the principle that PrP^{Sc} species with different conformations may be cleaved by proteases at different sites generating protease-resistant PrP^{Sc} fragments of different sizes, which then display different gel mobilities. This approach led to the discovery of two Syrian hamster prion strains, including the DY used by Peretz et al., and of the existence of at least two prion species in human prion diseases (Monari et al., 1994; Bessen and Marsh, 1994; Parchi et al., 1996). The two human prion species identified as PrP^{Sc} type 1 and 2 migrate on gel at 21 kDa and at 19 kDa, respectively, after deglycosylation. Interestingly, Peretz et al. also find the same gel mobilities for the Sc237 and DY prion strains as the human type 1 and 2, suggesting that, by this assay, Sc237 and DY match human PrP^{Sc} types. However, it has became obvious that the resolution of this assay is limited since prion strains that were definitely distinct belonged to the same type. More recently, three additional assays have been introduced. One is the analysis of prion strains by two-dimensional gel electrophoresis, which, by significantly increasing the gel resolution, demonstrates differences that are undetectable in one-dimensional gel electrophoresis (Pan et al., 2001). The other two are conformational assays including the conformational stability test used by Peretz at al. (2002) (Safar et al., 1998; Peretz et al., 2001). Although it is unquestionably powerful, the conformational assay used by Peretz et al. (2002) also seems to have limitations. For example, following a passage in the Tg(MH2M) mouse, the structural measurements of the Sc237 strain as determined by this assay become similar to those of DY strain, although the two strains are different by bioassay and by gel typing since Sc237 and DY remain of type 1 and 2, respectively, through the passages in the Tg(MH2M) mice. Because the insolubility and tendency to aggregate currently make the direct study of the three-dimensional structure of prion strains impossible, it is most likely that the best approach to examine the structural properties of the prion strains will be the use of multiple assays rather than one assay only. By using a combination of the available assays and new ones that will be undoubtedly developed in the future, we may shed light on the molecular mechanisms underlying the changes in the PrP^{Sc} conformation that then determine prion strain diversity and interspecies transmission.

The level of complexity of PrP^{Sc} conformation and interspecies prion transmission is staggering and may also depend on other factors, namely route of infection, PrP glycosylation, and other proteins interacting with PrP. Exciting and unexpected findings are likely to be forthcoming. Stay tuned.

Shu G. Chen and Pierluigi Gambetti
Institute of Pathology
Case Western Reserve University
Cleveland, Ohio 44106

Selected Reading

Bessen, R.A., and Marsh, R.F. (1994). J. Virol. *68*, 7859–7868.

Collinge, J. (2001). Annu. Rev. Neurosci. *24*, 519–550.

Gambetti, P., Parchi, P., Capellari, S., Russo, C., Tabaton, M., Teller, J.K., and Chen, S.G. (2001). J. Alzheimer's Dis. *3*, 87–95.

Monari, L., Chen, S.G., Brown, P., Parchi, P., Petersen, R.B., Mikol, J., Gray, F., Cortelli, P., Montagna, P., Ghetti, B., et al. (1994). Proc. Natl. Acad. Sci. USA *91*, 2839–2842.

Pan, T., Colucci, M., Wong, B.S., Li, R., Liu, T., Petersen, R.B., Chen, S., Gambetti, P., and Sy, M.S. (2001). J. Biol.Chem. *276*, 37284–37288.

Parchi, P.R., Castellani, R., Capellari, S., Ghetti, B., Young, K., Chen, S.G., Farlow, M., Dickson, D.W., Sima, A.A., Trojanowski, J.Q., et al. (1996). Ann. Neurol. *39*, 767–778.

Pattison, I.H. (1966). Res. Vet. Sci. *7*, 207–212.

Peretz, D., Scott, M.R., Groth, D., Williamson, R.A., Burton, D.R., Cohen, F.E., and Prusiner, S.B. (2001). Protein Sci. *10*, 854–863.

Peretz, D., Williamson, R.A., Legname, G., Matsunaga, Y., Vergara, J., Burton, D.R., DeArmond, S.J., Prusiner, S.B., and Scott, M.R. (2002). Neuron *34*, this issue, 921–932.

Prusiner, S.B. (1982). Science *216*, 136–144.

Prusiner, S.B., Scott, M., Foster, D., Pan, K.M., Groth, D., Mirenda, C., Torchia, M., Yang, S.L., Serban, D., Carlson, G.A., et al. (1990). Cell *63*, 673–686.

Prusiner, S.B. (1999). Development of the Prion Concept (Cold Spring Harbor, NY: Cold Springs Harbor Laboratory Press), pp. 67–112.

Safar, J., Wille, H., Itri, V., Groth, D., Serban, H., Torchia, M., Cohen, F.E., and Prusiner, S.B. (1998). Nat. Med. *4*, 1157–1165.

Adult Neurogenesis and the Vascular Nietzsche

Adult neurogenesis is mediated by immature neural precursors that divide within the residual germinal matrices of the brain. In the paper by Louissaint et al. (2002) in this issue of *Neuron*, the "cause and effect" of adult neurogenesis takes a major step forward with the description of a vascular signaling network that influences neuronal precursor migration and fate.

"Cause and effect: there is probably never any such duality; in fact there is a continuum before us, from which we isolate a few portions…. The suddenness with which many effects stand out misleads us; actually, it is sudden only for us. In this moment of suddenness there are an infinite number of processes which elude us."

—Nietzsche, 1882
Translated from "The Gay Science", section 112
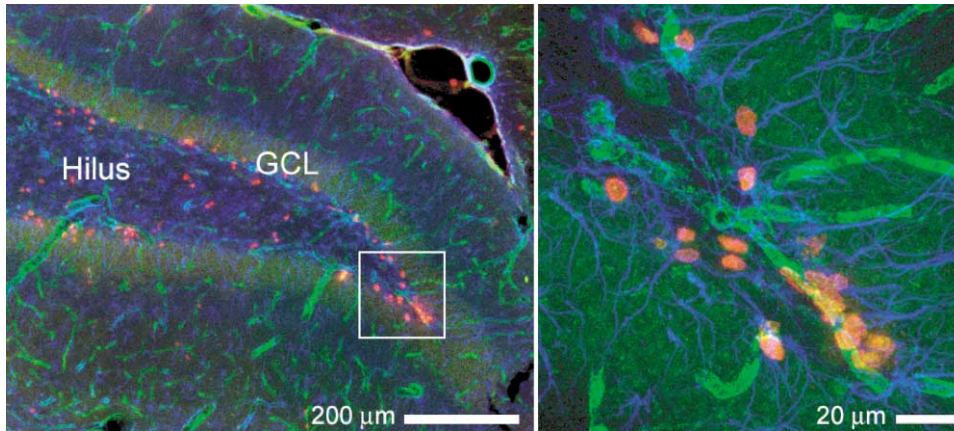
Neural Precursors Adjacent to Microcapillaries within the Adult Rat Dentate Gyrus

Bromodeoxyuridine-labeled nuclei of proliferative neural precursors (red) divide in close proximity to blood vessels (green) within the adult rat hippocampus. Precursors subsequently differentiate into granule cell neurons in the overlying granule cell layer (GCL). Endothelial cells (green) and astrocytes (blue) are the hypothetical "instructive" cells of the vascular niche.

From egg to adult, complex organisms arise from a continuum of cellular specialization and amplification. At each step, contextual cues refine and select functional programs from the genome's repertoire. At fertilization, the zygote becomes polarized. Cortical and internal cytoplasm flow in opposite directions relative to the incoming male pronucleus, and division across the plane of cytoplasmic asymmetry forges the first step in cellular differentiation. Intercellular communication is born. From this stage onward, a cell's intrinsic program is defined by its accumulated "experiences." These experiences become refined as increasingly specialized cells impart and receive signals from the local microenvironment.

In the developing central nervous system, examples of the instructive niche abound, but these defining cellular interactions also continue from birth to death where they mediate plasticity, adaptation, and repair. It has become apparent that the addition or replacement of neurons plays an integral role in adult brain function. In early work, Goldman and Nottebohm have shown that neurons of the vocal control nucleus of songbirds undergo a seasonal atrophy and rebirth (Goldman and Nottebohm, 1983; Nottebohm, 1985). Neurons of the higher vocal center (HVC) are lost and subsequently replaced in a cycle that is tightly modulated by estrogen and testosterone (Goldman and Nottebohm, 1983; Hidalgo et al., 1995). Neural precursors in the overlying ventricular zone are recruited into cycle early in the breeding season. The newborn neuroblasts migrate from the ventricular zone into the HVC where they mature and become functionally integrated. Goldman and colleagues also noted that angiogenesis was stimulated within the HVC and was coordinately regulated by gonadal steroids.

In mammals, adult neurogenesis is also mediated by stem cell-like precursors that remain within the vestigial germinal matrices of the adult brain. The emerging story of neurogenesis in the hippocampus is compelling. The hippocampus is notable for its role in learning and memory, and the processing of spatial information. New neurons are continuously added to the granule cell layer of the hippocampal dentate gyrus (Gould et al., 1999; Kuhn et al., 1996). These new neurons are functionally integrated (van Praag et al., 2002), and experimental manipulations that modulate neurogenesis have a clear impact on hippocampal function (Tanapat et al., 1998; van Praag et al., 1999).

Anatomically, the proliferative precursors within the adult hippocampus reside within a very thin lamina between the hilus and granule cell layer termed the subgranule zone (Kuhn et al., 1996). Within this lamina, neural precursors are recruited by unknown signals to divide. Proliferative cells reside in tight juxtaposition to the microcapillaries within the subgranule zone, and their mitogenic recruitment is accompanied by a concurrent angiogenic response (see Figure and see also supplemental movie at http://www.neuron.org/cgi/content/full/34/6/856/DC1; Palmer et al., 2000). Precursors in other areas of the hippocampal formation are also proliferative, but they are not found within this vascular niche and do not generate neurons. This has led to the speculation that the angiogenic microenvironment may be important for adult hippocampal neurogenesis and ultimately for hippocampus-mediated cognitive function.

In the groundbreaking study by Louissaint et al. (2002, this issue of *Neuron*), the vascular niche hypothesis gains substantial momentum and assigns the endothelial cell a leading role in promoting the maturation and survival of newborn neurons within the HVC of adult canaries. Louissant et al. tie neurogenesis and angiogenesis together in an elegant signaling network that involves testosterone, estrogen, vascular endothelial growth factor (VEGF), the avian VEGF receptor-2 homolog quek1, and brain-derived neruotrophic factor (BDNF). In female canaries, testosterone-releasing implants stimulate the upregulation of VEGF within the HVC. Quek1/VEGFR2 is coordinately upregulated within endothelium of the HVC. The combined outcome is a robust angiogenic response.

Subsequent to angiogenic stimulation, the endothelial cells elaborate brain-derived neurotrophic factor, which stimulates migration of the neuroblast from the ventricu-

lar zone and ultimately drives the maturation and survival of the newborn neurons within the HVC. The sequence of events is even more finely tuned by the local conversion of testosterone to estrogen by aromatase. The initial upregulation of VEGF expression appears to be solely responsive to estrogen, while the later expression of BDNF occurs via androgen-mediated transcriptional activation. The entire angiogenic process is self-regulated and resolves within 2 weeks, despite continuous elevations in testosterone.

Cells of mesenchymal origin have long been known to influence neural precursor cell fate, and Louissant et al. now draw endodermal cells into the fray. Although new players to the CNS instructive milieu, endothelial cells are also known for their influences in other organ systems. For example, prior to vascular formation, endothelial precursors lacking the mammalian VEGF receptor, flk-1, fail to populate the hepatic bud, and the amplifying cells of the liver primordia fail to acquire their normal hepatocyte identity (Matsumoto et al., 2001). In recriprocal experiments, Lammert and colleagues misexpressed VEGF under the control of Pdx1, a gene expressed in early gut and pancreas development, and observed hypervascularization within the transgene expression domains (Lammert et al., 2001). Ectopic production of islet cells accompanied the angiogenic response. Both observations indicate that endothelium play an important role in the early induction events in liver and pancreas.

To date, there is very little literature on the instructive role of the vasculature in CNS development, and the current observations by Louissant and colleagues may play the ironic role of triggering new studies in CNS development on the basis of observations made in the adult. Typically, the inverse is true. Developmental paradigms are finding a new home in adult studies of CNS plasticity and repair. Rapid advances in genomics, embryonic stem cells, and human therapy are driving a clear and well-deserved demand for information on how precursor cells function within the context of the adult.

Bringing the vasculature into the limelight as a modulator of adult neural precursor activity poses several very interesting questions. When contemplating the blockade or stimulus of angiogenesis for therapy, how will native precursor activity be affected? Will the chronic angiogenic blockade that is so promising in cancer therapies eventually lead to hippocampal dysfunction? What role do precursors play in the cognitive decline associated with angiopathies or vascular dimentia? Can physiological stimuli that perturb vascular biology affect cognition?

An interesting circularity of cognitive phenomena comes to mind. Hippocampal neurogenesis in the adult correlates with the hippocampal functions of learning and memory. Stress and chronic depression are accompanied by a decrease in hippocampal neurogenesis and degradation of hippocampal function (Cameron et al., 1998). Physical exercise is one of the most robust stimulators of neurogenesis and angiogenesis and is well known as an effective modulator of stress and depression (van Praag et al., 1999). What role might the vasculature play? Something to think about while I go out for a run . . . .

Theo D. Palmer
Stanford University
Department of Neurosurgery
MSLS P309, Mail Code 5487
Stanford, California 94305

Selected Reading

Cameron, H.A., Tanapat, P., and Gould, E. (1998). Neuroscience *82*, 349–354.

Goldman, S.A., and Nottebohm, F. (1983). Proc. Natl. Acad. Sci. USA *80*, 2390–2394.

Gould, E., Reeves, A.J., Graziano, M.S., and Gross, C.G. (1999). Science *286*, 548–552.

Hidalgo, A., Barami, K., Iversen, K., and Goldman, S.A. (1995). J. Neurobiol. *27*, 470–487.

Kuhn, H.G., Dickinson-Anson, H., and Gage, F.H. (1996). J. Neurosci. *16*, 2027–2033.

Lammert, E., Cleaver, O., and Melton, D. (2001). Science *294*, 564–567.

Louissaint, A., Jr., Rao, S., Leventhal, C., and Goldman, S. (2002). Neuron *34*, this issue, 945–960.

Matsumoto, K., Yoshitomi, H., Rossant, J., and Zaret, K.S. (2001). Science *294*, 559–563.

Nottebohm, F. (1985). Ann. NY Acad. Sci. *457*, 143–161.

Palmer, T.D., Willhoite, A.R., and Gage, F.H. (2000). J. Comp. Neurol. *425*, 479–494.

Tanapat, P., Galea, L.A., and Gould, E. (1998). Int. J. Dev. Neurosci. *16*, 235–239.

van Praag, H., Christie, B.R., Sejnowski, T.J., and Gage, F.H. (1999). Proc. Natl. Acad. Sci. USA *96*, 13427–13431.

van Praag, H., Schinder, A.F., Christie, B.R., Toni, N., Palmer, T.D., and Gage, F.H. (2002). Nature *415*, 1030–1034.