teine-rich domains (CRDs) similar to those of other family members, such as CD40, DR3, RANK, and the lymphotoxin-β receptor (see the figure) (*7*). Although the neurotrophin ligands share 50% amino acid sequence identity, they bear no resemblance to any TNF ligands. Nonetheless, the x-ray crystal structure of the CRDs in p75 is similar to that for the repeats of the p55 TNF receptor (*8*). However, for TNF/Fas family members, each ligand exists as a trimer that engages a trimeric receptor complex. The 2:1 NGF:p75 complex, therefore, is a major exception to the general rule of trimeric ligand-receptor complexes in this family.

What keeps p75 in a monomeric form when it binds to NGF? NGF itself forms a symmetrical homodimer generated by hydrophobic forces between a core of β-stranded sheets joined by three cysteine bridges (*9*). Two sites of interaction exist between the CRDs of p75 and each monomer of NGF in the x-ray crystal structure. This places p75 along a groove formed by the two monomers of NGF. Many individual contacts are formed by charge-charge interactions between positively charged basic residues found in NGF and the negatively charged extracellular domain of p75. Surprisingly, formation of this complex causes a conformation change in NGF such that a second p75 molecule is not able to make contact. NGF has two potential sites for receptor binding, but only one is used, resulting in an asymmetric NGF:p75 structure.

This unusual structure has many implications. It is well established that all neurotrophins can bind to p75. A sequence alignment indicates that similar points of contact with p75 are also found in the domains of BDNF, NT-3, and NT-4. The observed bending of NGF as it binds to p75 suggests that other neurotrophins also participate in conformational changes. Such allosteric events proposed by He and Garcia (*5*) are plausible, because the on and off p75 binding rates vary with each neurotrophin (*10*). Additionally, because proNGF has a higher affinity than mature NGF for p75 (*11*), other changes in conformation or stoichiometry may accompany the binding of proNGF to p75. The 2:1 NGF:p75 interaction also suggests that other molecules might be easily recruited to p75 to form higher order complexes. These include recently described interactions with membrane-associated proteins such as LINGO, Nogo receptor, and sortilin (*3*, *4*).

A particularly intriguing prediction of this model is that there is room for binding of Trk receptors to the NGF-p75 complex (see the figure). This mechanism had been proposed on the basis of reconstitution binding experiments showing that p75 and TrkA are responsible for high-affinity NGF binding sites (*12*). One can envision a heterodimer composed of p75 and a TrkA receptor binding to an NGF dimer, but the orientation of p75 would be opposite to that of TrkA. Although unconventional, this is nonetheless possible because p75 undergoes multiple cleavages that could release the extracellular ligand-binding domain. Moreover, changes in the conformation of TrkA also can occur (*2*).

During development, the binding of neurotrophins to their receptors is of paramount importance in matching the correct number of neurons with their targets. The NGF family also regulates axonal and dendritic growth, the formation of synaptic structure and connections, neurotransmitter release, and long-term potentiation. Alterations in neurotrophin levels may underlie several medical conditions, including pain, depression, obesity, and disorders in nerve regeneration, learning, and memory (*2*). Therefore, this glimpse of NGF binding to p75 offers the opportunity to begin to think about therapeutic drug design, a goal that has thus far eluded the trophic factor field.

References

1. E. Huang, L. Reichardt, *Annu. Rev. Biochem.* **72**, 609 (2003).
2. M. V. Chao, *Nature Rev. Neurosci.* **4**, 299 (2003).
3. S. Mi *et al.*, *Nature Neurosci.* **7**, 221 (2004).
4. A. Nykjaer *et al.*, *Nature* **427**, 843 (2004).
5. X.-l. He, K. C. Garcia, *Science* **304**, 870 (2004).
6. C. Wiesmann, M. Ultsch, S. Bass, D. Vos, *Nature* **401**, 184 (1999).
7. R. Locksley, N. Killeen, M. Lenardo, *Cell* **104**, 487 (2001).
8. D. W. Banner *et al.*, *Cell* **73**, 431 (1993).
9. N. Q. McDonald *et al.*, *Nature* **354**, 411 (1991).
10. M. Bothwell, *Annu. Rev. Neurosci.* **18**, 223 (1995).
11. R. Lee, P. Kermani, K. Teng, B. Hempstead, *Science* **294**, 1945 (2001).
12. B. L. Hempstead, D. Martin-Zanca, D. R. Kaplan, L. F. Parada, M. V. Chao, *Nature* **350**, 678 (1991).

GEOPHYSICS

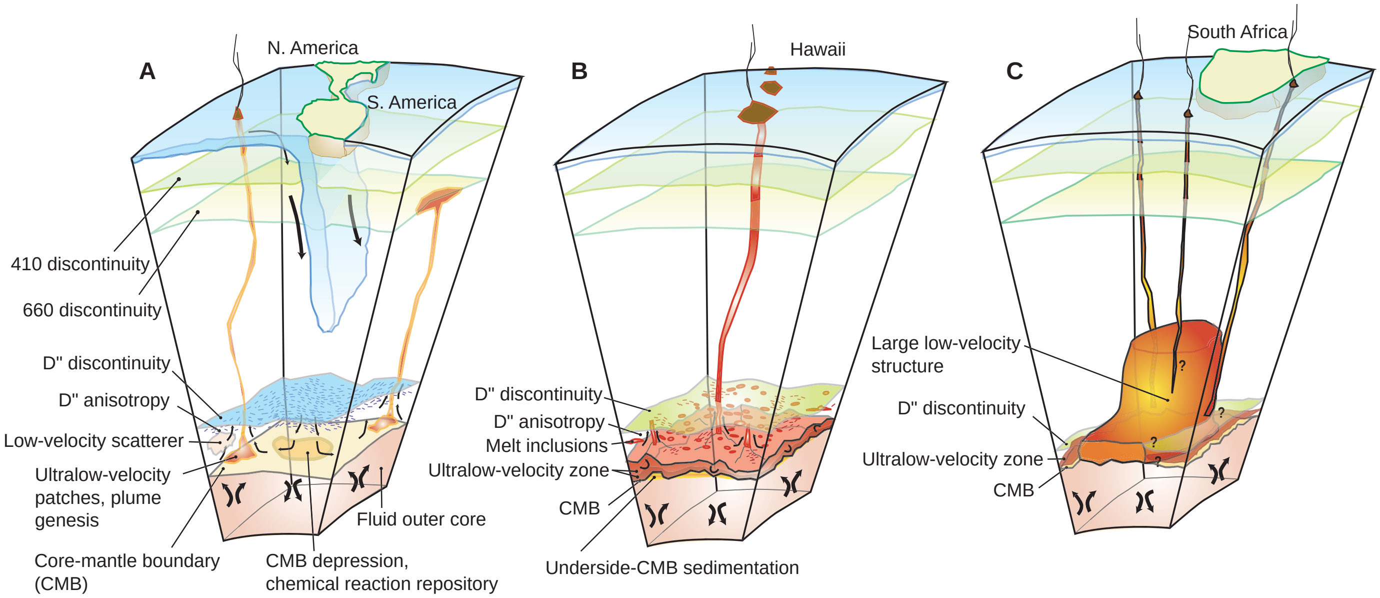
A New Paradigm for Earth's Core-Mantle Boundary

Edward J. Garnero

At a depth of about 2900 km, the solid silicate rock of Earth's mantle meets the liquid iron alloy of the core. This region, called the core-mantle boundary (CMB), has long been pictured as a simple dividing zone. Recently, however, this neat model has been directly challenged by a broad range of discoveries. These include exciting new evidence for a deep-mantle phase change as reported by Murakami *et al*. on page 855 of this issue (*1*), layering in the lowermost mantle (*2*), partial melting (*3*), mineral anisotropy (*4*), and small-scale convection with formation of whole-mantle plumes (*5*, *6*). Because of these findings, researchers have created a new paradigm, in which deep-mantle layering and heterogeneity exist globally, with notable regional variations. This heterogeneity is intimately coupled to important processes of the interior, such as modulating heat flow out of the core, and hence fluid core convection currents, and the magnetic field (particularly during reversals) (*7*). The CMB may also act as a repository for lighter elements that emerge from the core fluid (*8*). These phenomena are all consequences of the largest absolute temperature and density contrasts within the planet. Although many of the details of this new paradigm remain enigmatic, the growing body of evidence suggests that the deepest mantle and CMB contain the same degree of chemical, dynamical, structural, and thermal complexity as that of Earth's surface, and hence likely hold important clues for deciphering the evolution and present state of the entire interior.

The author is in the Department of Geological Sciences, Arizona State University, Tempe, AZ 85287–1404, USA. E-mail: garnero@asu.edu

For more than two decades, it has been recognized that the top and bottom few hundred kilometers of Earth's rocky mantle contain the planet's strongest seismic heterogeneity over long lateral distance scales (>2000 km) (*9*). Several recent (and upcoming) conference proceedings as well as a special journal issue (*10*) highlight seismic analyses that image the deep mantle and CMB region at much shorter scales, around hundreds of kilometers laterally and sometimes less than tens of kilometers vertically. Partly owing to Earth's limited geographical distribution of earthquakes and recorders, only isolated patches of the deep mantle can be investigated at this level of detail. Three of the most thoroughly studied regions are (i) beneath Central America and the Caribbean Ocean, an area underlying past and present subduction that is grossly characterized with higher



Emerging view of Earth's interior. Deep-mantle complexities are illustrated for three regions: (**A**) Beneath Central America, the deepest mantle contains a high-velocity D″ reflector, and localized scatterers of seismic energy that may be related to pockets of ultralow velocities and possibly plume formation, and strong anisotropy. (**B**) Beneath the central Pacific, which underlies surface hotspot volcanism, abundant evidence exists for D″ anisotropy and ultralow-velocity zones, as well as possible plume genesis, a mild D″ high-velocity reflector, and core-rigidity zones. (**C**) Beneath the south Atlantic and southern Africa, a large-scale low-velocity structure with sharp edges extends upward into the lower mantle, and may exist independently of neighboring D″ material. These three locales exemplify the new CMB paradigm of a structurally and dynamically rich CMB region.

than average seismic velocities; and two regions where several hotspot volcanoes litter the surface (ii) beneath the central Pacific Ocean and (iii) beneath the southern Atlantic Ocean. The distribution and magnitude of inferred seismic heterogeneity, anisotropy, and layering differ significantly between these regions. The figure incorporates many of the findings and suggestions of the CMB region for these locations, which are briefly reviewed here.

A discontinuous increase in seismic wave speeds atop the lowermost 200 to 300 km above the CMB (a range in depth called D″) has been documented in several regions on the planet, and is most easily detected beneath regions near past subduction, for example, beneath Central America, particularly for shear waves (panel A in the figure). Such a reflector has been noted beneath the Pacific Ocean as well (panel B), but is not as strong. Beneath the south Atlantic Ocean, a strong reduction in velocity is found near the top of D″ (panel C). The latter two regions have not experienced subduction recently, and are hence expected to be warmer. A model reconciling the magnitude of the reflector (with an *S*-wave velocity that is 2 to 3% above average in cooler D″ regions to a 2 to 3% below-average velocity in the hottest regions) assumes a D″ layer that is chemically distinct from the bulk lowermost mantle with some constituent close to eutectic melting (*2*). The magnitude and sign of the velocity discontinuity, therefore, may be a manifestation of the degree of D″ partial melting. Additionally, but not necessarily negating this possibility, the material composing the low-velocity anomaly beneath the south Atlantic may itself be chemically distinct from the rest of D″ (*11*), implying a chemically unique lowermost mantle with lateral variations in chemistry.

An alternative (or in addition) to a thermo-chemical layer as the origin of the D″ discontinuity is a phase change in perovskite (thought to be the most abundant mineral structure in the lower mantle). The in situ x-ray diffraction measurements of $MgSiO_3$ by Murakami *et al.* (*1*) demonstrate the feasibility of a phase change from perovskite to a denser structure at pressures corresponding to this depth. Although the Clapeyron slope and the effect of iron are not constrained at present, these results are far-reaching, because the post-perovskite structure is expected to be strongly anisotropic, in agreement with a seeming abrupt onset to D″ anisotropy. Future work will determine the applicability of this result to the different D″ geographies and their detailed velocity structures.

Delays between horizontally and vertically polarized shear waves (shear-wave splitting) that propagate through D″ have been observed nearly everywhere that high-quality core-reflected, refracted, or diffracted data have been analyzed. Thus, seismic wave–speed anisotropy in the lowermost 200 to 300 km of Earth's mantle is present, but is apparently quite variable (*12*). These results are compatible with new geodynamic calculations that show strain-induced recrystallization and lattice-preferred crystal orientation related to overlying subduction (beneath downwellings such as that shown in panel A), and fabric development due to strong boundary-layer shear flow beneath upwelling currents (as in panel B) (*4*). Shear-wave splitting has not been reported for D″ beneath the south Atlantic, within the large low-velocity feature. Future work should focus on better constraining the depth distribution of anisotropy within the D″ layer, as well as its magnitude and most plausible mechanism in the diverse settings depicted in the figure, and also how high strains in D″ affect the post-perovskite assemblage.

Both seismology and mineral physics have provided evidence for a partially molten ultralow-velocity zone (ULVZ) a few to tens of kilometers thick, right at the CMB in certain regions (*3*, *8*, *10*). The level of velocity perturbations associated with this probably intermittent layer is the largest within the planetary interior (≥10 to 30% reductions in seismic wave speed), in some cases even exhibiting its own internal layering (*3*). The lowest velocity regions of the deep mantle may be intimately related to ULVZs, which likely modulate heat flow from the core. In the hottest regions of D″, melt may be convectively stirred throughout D″, as suggested in panel B of the figure. Preferred orientation of melt pockets or sheets can give rise to observed shear-wave splitting (*12*). Although the shear velocities at the base of the large low-velocity province in panel C are indeed low, they are not characterized as a ULVZ, because minimal *P*-wave anomalies are detected; this low-velocity structure may be distinct from the rest of D″ (as suggested in the figure), because its sharp and steep sides within D″ imply its abrupt onset and uniqueness from its surroundings (*11*), which cannot be explained with solely thermal scenarios—introduction of chemically unique material is necessary. Evidence also exists for anomalous material on the fluid core side of the CMB (*13*), which might be related to underside-CMB sedimentation (*8*). Future work should adopt a multiphase approach—one that incorporates both diffracted and reflected energy, in order to better constrain the bulk properties and sharpness of ULVZ features.

In some D″ locations beneath subduction, as well as hotspots (all panels of the figure), evidence has mounted for small-scale inhomogeneities or scatterers (<10 km to hundreds of km) from a variety of seismological probes, such as precursors to coda arrivals to core reflected, refracted, and diffracted *P* and *S* waves of all types (*14*). Although not now well constrained, these may include the aforementioned pockets of ULVZ material at the CMB and possible mid-D″ low-velocity structures (such as depicted in panel A), ULVZ melt material swept around D″ (panel B, for example), and topographical variations at comparable lateral scales for the D″ discontinuity or ULVZ, which are expected at scales comparable to convective currents within and above the layer.

Although the environments schematically illustrated in the panels of the figure are certainly very different from one another, they probably represent only a subset of deep-mantle possibilities. A framework that ties them together involves strong lateral variations in temperature and partial melt content, as well as composition, which should modulate the topographical structure and dynamical behavior of a global D″ layer (*2*). These lateral perturbations can govern variations in heat flow from the core, and thus the vigor and style of internal D″ and overlying convection, including the birth of mantle plumes, D″ anisotropy, and ultralow velocities right at the CMB.

If the phase change discussed by Murakami *et al*. (*1*) corresponds to the top of D″, it may certainly provide unanticipated explanations to many observations, including the geometry of D″ anisotropy, the strength and degree of mineral alignment, the relation (difference) between *P*- and *S*-wave discontinuity strength, and the geometry of melt within D″. Other important avenues to be explored will be investigations of possible temperature-dependent iron partitioning into or out of the new post-perovskite phase, and better constraints on the Clapeyron slope, each of which are far-reaching.

Community interest in advancing our knowledge in this arena is reflected in the success of the National Science Foundation's *Cooperative Studies of the Earth's Deep Interior* (CSEDI) program (*15*), which funds multidisciplinary research on the structure and dynamics of Earth's interior, particularly aimed at processes that affect Earth's surface. Future analyses will bring into better focus the details of this new CMB paradigm through such a multidisciplinary approach.

References and Notes

1. M. Murakami *et al.*, *Science* **304**, 855 (2004); published online 8 April 2004 (10.1126/science.1095932).
2. T. Lay, E. J. Garnero, Q. Williams, *Phys. Earth Planet. Int.*, in press.
3. S. Rondenay, K. Fischer, *J. Geophys. Res.* **108**, 2537, 10.1029/2003JB002518 (2003).
4. A. K. McNamara, P. E. van Keken, S. Karato, *J. Geophys. Res.* **108**, 2230, 10.1029/2002JB001970 (2003).
5. P. J. Tackley, *Geochem. Geophys. Geosyst.* **3**, 10.1029/2001GC000167 (2002).
6. R. Montelli *et al.*, *Science* **303**, 338 (2003).
7. P. Olson, in *Earth's Core and Lower Mantle*, C. A. Jones, A. M. Soward, K. Zhang, Eds. (Taylor and Francis, London, 2003), chap. 1, pp. 1–38.
8. B. A. Buffett, E. J. Garnero, R. Jeanloz, *Science* **290**, 1338 (2000).
9. G. H. Masters, A. M. Bolton, A. M. Dziewonski, G. Laske, in *Earth's Deep Interior: Mineral Physics and Tomography from the Atomic to the Global Scale*, S. Karato, A. M. Forte, R. C. Liebermann, G. Masters, L. Stixrude, Eds. (American Geophysical Union, Washington, DC, 2000), pp. 63–87.
10. Meeting of the American Geophysical Union, 8 to 12 December 2003; Symposium on the Study of the Earth's Deep Interior, 4 to 9 July 2004; and Special Issue on Geophysical and Geochemical Evolution of the Deep Earth: SEDI 2002, *Phys. Earth Planet. Int.* **140**, 1 (2003).
11. S. Ni, D. V. Helmberger, *Phys. Earth Planet. Int.* **140**, 243 (2003).
12. M. Moore, E. J. Garnero, T. Lay, Q. Williams, *J. Geophys. Res.* **109**, B02319, 10.1029/2003JB002546 (2004).
13. S. Rost, J. Revenaugh, *Science*, **294**, 1911 (2001).
14. F. Niu, L. Wen, *Geophys. Res. Lett.* **28**, 3557 (2001).
15. www.geo.nsf.gov/cgi-bin/geo/showprog.pl?id=17&div=ear
16. This work is supported by National Science Foundation grant EAR0135119.

BIOPHYSICS

Catching Copper in the Act

Nermeen W. Aboelella, Anne M. Reynolds, William B. Tolman

Metalloproteins are involved in biological processes ranging from energy transduction, to cellular signaling, to modification of organic substrates. These processes often depend on the binding, activation, or generation of simple diatomic molecules like O_2, N_2, H_2, NO, and CO at the active-site metal ion(s) (*1*). The metal-diatom adducts are fleeting intermediates in the catalytic pathways, making them difficult to characterize. However, knowing their chemical properties is key to understanding how the metalloenzymes function. In this issue, Tocheva *et al*. on page 867 (*2*) and Prigge *et al*. on page 864 (*3*) describe x-ray crystal structures of reactive intermediates in two important copper enzymes. Novel coordination geometries of O_2 and NO each bound to a single copper ion provide intriguing mechanistic insights and set the stage for further synthetic and biological study.

In generating nitric oxide (NO) from nitrite (NO_2^-) during anaerobic bacterial metabolism (see the figure), the copper-containing nitrite reductase (NiR) plays a key role in the global nitrogen cycle. Previous studies of NiR in its resting state revealed three histidine ligands and a water molecule coordinated to the catalytic Cu(II) center (*4*, *5*). Nitrite binds at this center and is converted to NO, presumably via a copper-nitrosyl intermediate ($[CuNO]^{2+}$), although this has not been observed. Indeed, structurally defined copper-nitrosyls are rare, the only monocopper examples being in amine oxidase (*6*) and a synthetic complex LCuNO (L, tridentate anionic ligand) (*7*), both of which feature end-on coordination of the NO ligand through the N atom. Now, Tocheva *et al*. (*2*) show that treatment of reduced NiR with NO in the absence of excess reductant yields a stable copper-nitrosyl ($[CuNO]^{+}$) that features side-on coordination with the copper binding to both the N and O atoms (see the figure). The observation of side-on binding is striking, because although it is established for synthetic O_2 adducts of copper (*8*, *9*), such a binding mode for NO has only been seen in metastable complexes of other metals trapped at low temperatures (*10*, *11*). On

The authors are in the Department of Chemistry and Center for Metals in Biocatalysis, University of Minnesota, Minneapolis, MN 55455, USA. E-mail: tolman@chem.umn.edu