terol itself might be needed to support the structural demands of synaptogenesis. For example, cholesterol binds to several synaptic proteins, and is necessary for the formation of synaptic vesicles and for the clustering of certain postsynaptic receptors (*10*–*12*).

But perhaps the most important question is whether the glial delivery of cholesterol to neurons within the brain is the limiting factor regulating synapse formation. Cholesterol within the brain is derived almost entirely through in situ synthesis by brain cells (*13*). The appearance of most synapses in the developing brain is temporally and spatially coincident with the development of astrocytes, suggesting that synapse formation may depend on astrocyte-derived cholesterol (*2*). It is possible that once astrocytes begin to develop, neurons always have plenty of cholesterol available to them in vivo. On the other hand, glia have recently been found to control synapse number within the developing cerebellum of transgenic mice whose glia express mutant glutamate receptors (*14*). These findings are consistent with the possibility that astrocytes, by providing a limiting cholesterol supply to neurons, control synapse formation in vivo.

Could the cholesterol supply also regulate synaptic plasticity in the adult brain? Although astrocytes are needed to maintain synapses formed in culture, it is not yet clear whether cholesterol is similarly required. The LDL receptor–related protein (LRP), however, has been directly implicated in synaptic plasticity in hippocampal slices (*15*). Even more intriguing, apoE has long been suspected to be involved in neurodegenerative loss of synaptic plasticity in Alzheimer's disease (*16*). The apoE4 isoform is associated with an increased risk of late-onset Alzheimer's disease and is less able to promote neurite outgrowth than other apoE isoforms (*17*). Will apoE4 also differ in its ability to promote synapse formation? Fortunately, identification of cholesterol as the glial-derived synapse-promoting signal should make it possible to investigate the involvement of cholesterol and glia in synaptic development and plasticity in vivo.

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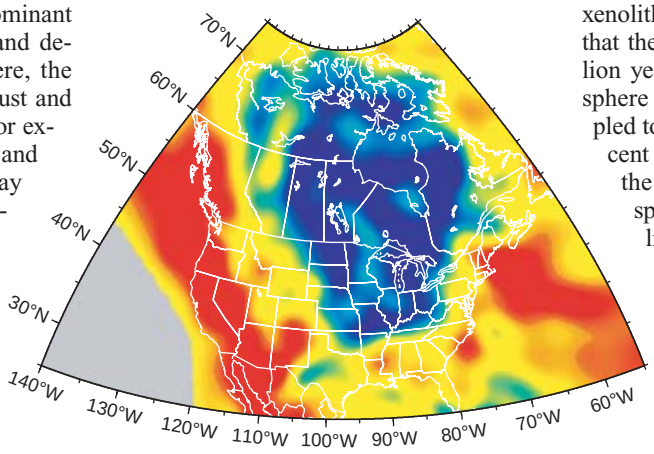
PERSPECTIVES: GEOLOGY

Deep Below North America

Suzan van der Lee

Today, plate tectonics is the dominant process behind the creation and destruction of Earth's lithosphere, the stiff outer layer that includes the crust and the uppermost part of the mantle. For example, as the South American Plate and the African Plate are moving away from one another, lithosphere is created in the central South Atlantic and begins to be destroyed in the subduction zone beneath the Andes. Was plate tectonics also a dominant process in Earth's early history? To answer this question, we must study the oldest parts of today's lithosphere.

The oldest rocks on Earth are found in the Slave Province, a geological region in the Northwest Territories, Canada. These rocks formed 4030 million years ago (*1*, *2*)—only about 500 million years after the formation of the solar system and 3900 million years before Gondwanaland broke up into Africa and South America. Practically all rocks and geological structures of the Slave Province are older than 2500 million years, and the area has been tectonically undisturbed ever since (*3*).



Geophysical map of North America. The blue and red shades are a proxy for the stiffness of mantle rocks at a depth of 140 km; blue represents the stiffest material. This map was produced as part of an ongoing collaboration (*5*, *6*) and is based on the analysis of over 1200 seismograms from different seismographic networks in North America. The large blue region roughly represents the part of North America that is older than 1000 million years and is called Laurentia.

Geophysical observations indicate that North American Provinces that are older than 1000 million years, including the Slave Province, generally have a cold, stiff lithosphere (*4*) that is 250 km thick on average (*5*, *6*). Some rocks, called mantle xenoliths, have been brought to the surface from deep within this thick lithosphere by rapidly ascending gas-rich magmas. In the Slave Province, these magmas also carried diamonds to the surface, suggesting that the deep lithosphere could be as old as the crust. Indeed, recent analyses of mantle xenoliths from the Slave Province indicate that the deep lithosphere is over 2500 million years old (*7*, *8*). This old, deep lithosphere has thus remained physically coupled to the overlying crust during more recent plate tectonic processes, leading to the widespread use of the term tectosphere (*4*) for such thick, continental lithosphere.

The tectosphere is characterized by relatively low temperatures because it has not participated in mantle convection for hundreds to thousands of millions of years. Furthermore, it is relatively depleted in iron (*4*), preventing it from sinking into the deeper mantle. The low temperature causes the tectosphere to be stiffer than the average upper mantle, resulting in faster propagation of seismic waves through the tectosphere. Seismic waves that traversed the continent can be combined into a three-dimensional map of seismic wave speeds, which may be considered to first order as a proxy for stiffness—and temperature (*9*)—of the North American upper mantle (see the figure).

The large blue area in the figure is roughly coincident with Laurentia (*3*, *10*), the predecessor of the present North American continent. Laurentia consists of a large

The author is in the Institute for Geophysics, Eidgenössische Technische Hochschule Honggerberg (HPP), CH-8093 Zurich, Switzerland. E-mail: suzan@tomo.ig.erdw.ethz.ch

number of geological terranes of different ages. Several terranes are of Archean age (the age of the Slave Province). They are welded together by younger terranes that formed in the Proterozoic, between 2500 million and 1000 million years ago.

The Laurentian terranes differ not only in age but also in lithospheric composition, temperature, and thickness. Large-scale geochemical and geophysical studies indicate that the Proterozoic lithosphere is less depleted in iron (*9*) and aluminium (*11*) than the Archean lithosphere. Some Archean tectosphere is thicker than the Proterozoic one but another Archean province, Wyoming, no longer has any thick lithosphere (*5*) (see the figure). On smaller scales, the picture is much more complicated. Moreover, the heterogeneity within Laurentia is not only horizontal. Composition and stiffness also vary with depth, indicating that the formation of Archean and Proterozoic tectosphere was not a simple process.

Models for tectosphere formation and evolution invoke many different processes, such as the cooling of extremely high-temperature mantle melts (for example, from upwelling mantle plumes), the stacking of buoyant Archean lithospheric plates, and processes much like today's plate tectonics, including subduction of the lithosphere. Deep probing of the tectosphere is providing clues as to which of these processes played a role in the evolution of today's lithosphere.

Programs such as Lithoprobe (*12*) have provided important insights into the structure and evolution of continental lithosphere in Canada. Results from Lithoprobe investigations of different parts of the Laurentian crust point to an important role for subduction in the formation and evolution of tectosphere younger than 3000 million years. Laurentia, which is only half the size of North America (see the figure), was assembled by such processes by 1000 million years ago (*10*). Geological similarities between various Archean provinces around the world indicate that a form of plate tectonics may have operated in the Archean, with "protoplates" that were much smaller than Laurentia or present-day tectonic plates. For example, the Slave and Wyoming Provinces may have been part of one larger "protocontinent," Sclavia, together with the Archean Zimbabwe Province of southern Africa and the Dharwar Province in India around 2600 million years ago (*2*). In addition, hot upwellings from the deep mantle may also have contributed to the evolution of the North American tectosphere, for example, in the mid and late Archean (*3*, *7*).

Lithoprobe is one of the main reasons why we now know so much about the Laurentian crust, and continental-scale geophysical studies have provided three-dimensional images of the uppermost mantle beneath Laurentia, although not nearly at the same level of detail as the crustal studies. More research is necessary to establish how Archean and Proterozoic lithosphere formed and evolved. New geophysical experiments need to characterize the Laurentian tectospheric mantle in more detail, for example, through the deployment of dense networks of broadband seismometers. It is also important to broaden our study areas—to include tectosphere worldwide, for example, in southern Africa, and to integrate analyses from multiple disciplines. Focusing and broadening our research efforts in this way will help unravel some of Earth's early geological history.

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13. I thank the organizers and the sponsors of the Slave-Kaapvaal workshop (www.cg.nrcan.gc.ca/slave-kaapvaal-workshop/), Merrickville, Canada, for supporting my participation in the workshop.

NOTA BENE: MICROBIOLOGY

Know Thine Enemy

The anthrax bacillus is enjoying renewed notoriety as an agent of bioterrorism. Inhalation of about 10,000 *Bacillus anthracis* spores causes a systemic form of anthrax that is fatal unless treated immediately with antibiotics. This lethality is principally due to the tripartite toxin produced by the anthrax bacillus. Assembled on the surface of host cells, this toxin is composed of protective antigen (PA) bound to two enzymes, lethal factor (LF) and edema factor (EF), which block macrophage activity. Two recent *Nature* papers identify the host cell receptor for PA (*1*) and reveal the structure of LF (*2*), providing hints about targets for therapeutic intervention in the later stages of the disease.

LF and EF depend on PA for access to their intracellular targets. The PA heptamer enters the cell by endocytosis, taking LF and EF along with it. The low pH of host cell endosomes induces a conformational change in PA, which enables LF and EF to cross the endosomal membrane and to enter the cell cytosol. LF, a metalloprotease, cleaves different isoforms of the MAPKK signaling molecule causing macrophages to lyse; EF, an adenylate cyclase, blocks phagocytosis of anthrax bacilli by macrophages.

The host cell receptor bound by PA is a potential target for therapeutic intervention. Using a genetic complementation approach, Bradley *et al*. (*1*) show that the cellular receptor for PA (called ATR) is a type I integral plasma membrane protein of unknown function that contains an extracellular von Willebrand type A (VWA) domain. Soluble VWA can block binding of PA to ATR suggesting one strategy for preventing toxin entry (assuming that ATR is the only cellular receptor).

Pannifer and colleagues (*2*) have refined the crystal structure of LF to 2.2 Å resolution. Of LF's four domains, domain I contains a docking site for PA, and domains II and III interact with domain IV to form an extended binding pocket that is specific for the MAPKKs. With the LF structure in hand, it should be possible to screen small molecules for their ability to block binding of MAPKKs to LF. Neutralizing the effects of LF could provide a therapeutic means for treating the systemic stages of the disease.

As an added bonus, understanding how the anthrax toxin enters cells should help in fine tuning lethal toxin, a combination of PA and LF, which has proven to be an effective antitumor agent in the test tube and in animals. **–ORLA SMITH**

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