synaptic terminals of dopaminergic neurons, where there are high concentrations of dopamine, parkin and α-synuclein, and where mitochondrial alterations are believed to be pivotal to the neurodegenerative process[13,14]. However, the protein synthetic ER (and presumably PDI) is present in much higher amounts in the dendrites and cell body as compared to the axon terminals[15]. Similarly, NMDA receptors and NOS are concentrated in dendrites, suggesting that nitrosylation of PDI occurs mainly in dendrites. The findings of Uehara *et al.* therefore provide new evidence for dendritic abnormalities in the pathogenesis of Parkinson disease.

The importance of PDI impairment in the abnormal protein accumulations and neuronal death in Parkinson disease, relative to other mechanisms (mitochondrial impairment, oxidative stress, proteasome dysfunction and others), remains to be established. Nevertheless, PDI is a newcomer to the list of potential targets for therapeutic intervention in Parkinson disease and other protein aggregation disorders. Several possible approaches can be envisioned, including drugs that induce the expression of PDI or enhance its enzymatic activity, agents that block *S*-nitrosylation of PDI, such as general scavengers of NO or selective inhibitors of PDI nitrosylation, and agents that inhibit NO production. Because NO is believed to be important in other neurodegenerative disorders, such as Alzheimer disease, Huntington disease, amyotrophic lateral sclerosis and stroke, among others, it is important to determine whether NO-mediated impairment of PDI function is also critical for the abnormal accumulation of protein garbage and neuronal death in these disorders.

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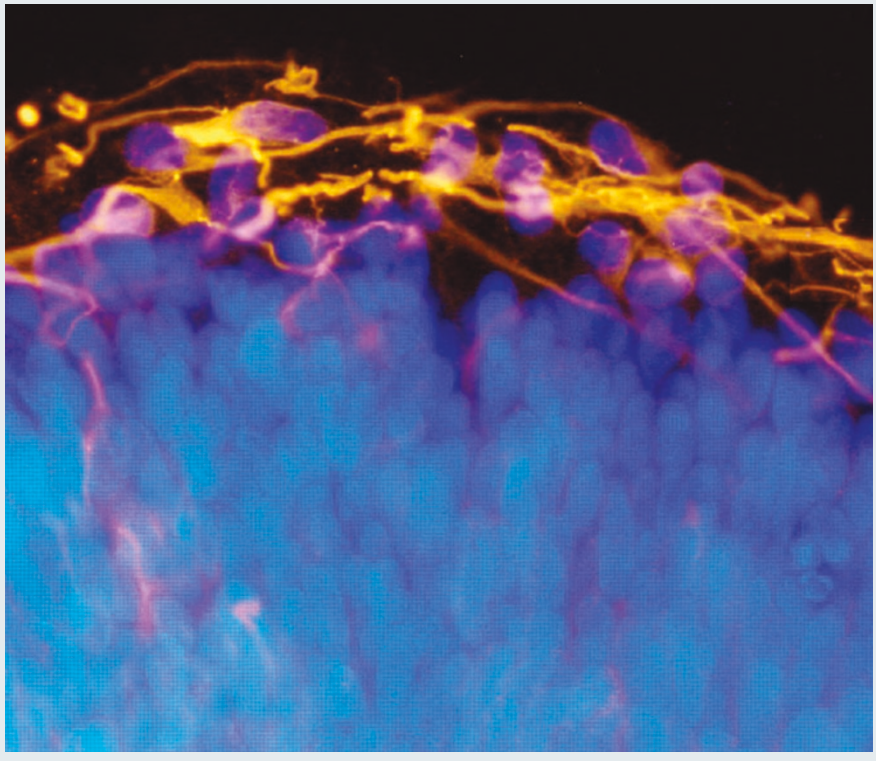
Trailblazers of the cortex



On page 880 of this issue, there is a paper with the grand title "The first neurons of the human cerebral cortex." In rare specimens of human embryos aborted in the fifth week of development, before the neural tube is even fully closed, Bystron and colleagues were able to detect cells that look convincingly like neurons and express the established neuron marker βIII-tubulin. The cells are found in the prospective cortex, in a layer just below the pial surface of the incipient telencephalon, before any neurogenesis takes place in the local telencephalic neuroepithelium. It appears as though these cells enter the telencephalic domain tangentially from underlying areas, though their exact origin remains unclear. The authors call these cells "predecessor neurons." The image shows these neurons, stained golden for βIII-tubulin, on top of the as-yet undifferentiated telencephalic ventricular zone from a 35-day-old human embryo. The blue stain labels all nuclei.

The earliest cortical neurons have been widely assumed to be the Cajal-Retzius cells, which also spread across the telencephalic surface after tangentially migrating long distances from their birthplaces. Cajal-Retzius cells are most famous for their expression of reelin, which is crucial in guiding the development of the stratified neocortex. The predecessor neurons make no reelin, however, and are thus an entirely new neuron population. Furthermore, the first Cajal-Retzius cells in the emerging human cortex appear a week later than the predecessors. The authors show predecessor and Cajal-Retzius neurons coexisting in the primordial plexiform layer of 7-week-old embryos, with Cajal-Retzius cells coming to lie in the emerging marginal zone above the predecessors.

The new predecessor neurons raise many, many questions. What is their origin, and what is their function? How long do they persist in the developing brain? Could the cortex develop without them? To tackle these issues, analogous early cortical neurons would need to be identified in experimentally amenable species. Unless, of course, the predecessor neurons turn out to be specific to higher primates, which would make them especially interesting. In any case, Bystron and colleagues have opened a new chapter in the developmental biology of the brain, and we eagerly await the sequel.

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