she expects to occur in humans as well. But some in the field caution against making that leap from these data until there is an explanation for Rakic's negative result in rhesus monkeys. "The idea that they can extrapolate on to humans is blocked in part" by Rakic's results, says Salk's Gage.

Gould counters that Rakic used a different—and less sensitive—method for detecting new neurons and thus might have missed their formation. Rakic acknowledges that his group could have overlooked a low level of neuron production but says "certainly we would not miss several thousand a day."

The issue will remain open, says Harvard neuroscientist Connie Cepko, until more tests on primates, including a reexamination of rhesus monkeys with the newer methods, are performed. "If one monkey species does it and one doesn't, we can't extrapolate to [humans]," she says, "but if all monkeys do it," such an extrapolation would seem a safer bet. Some researchers aren't waiting to make their wagers: "I'll make a bet," says McKay. "This is going to happen in humans. The question is under what circumstances, and what difference does it make?"

Indeed, "one of the challenges for this field is to try to come up with some biological significance for this late-stage neurogenesis," says Gage. That significance, says Stanford neuroscientist Susan McConnell, hinges on the question, "What is the actual result of putting new neurons into a circuit? Does it, for example, help you learn or remember better?" If it does, psychologists and neuroscientists will have a field day putting these results to practical use.

–Marcia Barinaga

DEVELOPMENTAL BIOLOGY

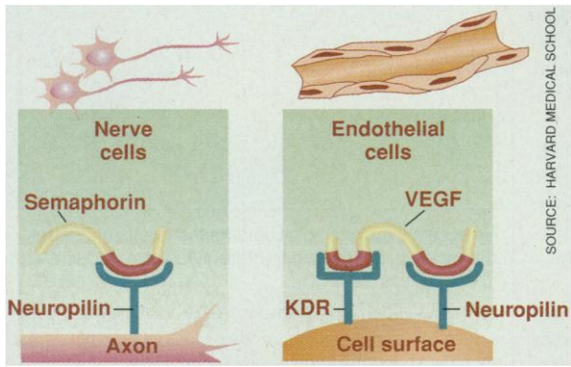
Receptor Links Blood Vessels, Axons

Veins gather blood and return it to the heart, Leonardo da Vinci mused in one of his notebooks, in the same way that rivers channel water back to the oceans. But a recent discovery suggests that da Vinci's analogy was more impressionistic than accurate. Rather than following random paths like water trickling downhill, it appears that blood vessels may instead use detailed chemical cues to navigate to prearranged addresses—much as nerves do.

In the 20 March issue of *Cell*, a group led by biochemist Michael Klagsbrun at Children's Hospital in Boston reports that it has identified a new receptor molecule on the endothelial cells that line blood vessels. The receptor, called neuropilin, picks up a signal from VEGF, a protein made by tissues—including cancerous tumors—that need new blood vessels. VEGF was already known to stimulate blood vessel growth, or angiogenesis, but most researchers thought the actual paths of the vessels are as random as da Vinci's watercourses. The new receptor, however, turns out to be the same one that nerve axons use to detect Semaphorin III, a protein that helps steer axons to their proper destinations in the developing nervous system.

"It's a very exciting discovery," says Marc Tessier-Lavigne, a developmental biologist at the University of California, San Francisco, whose laboratory, along with one in Baltimore, identified the semaphorin receptor last year. The receptor's dual role, he says, raises the intriguing possibility that angiogenesis, far from being random, is in fact as highly scripted as axonal pathfinding, which is regulated by a whole menagerie of extracellular messengers in addition to Semaphorin III. He and Klagsbrun also note that if neuropilin allows VEGF to act on neurons and semaphorins to act on endothelial cells, this might indicate an unexpected level of coordination between the developing nervous and circulatory systems. The discovery, finally, could even provide researchers with a new target for drugs that might fight cancer by blocking tumor growth.

Shay Soker, an instructor in Klagsbrun's lab and the *Cell* paper's lead author, cleared the way for the recent advance in experiments he performed 2 years ago. Using a biochemical technique called crosslinking, Soker found that VEGF forms two different kinds of complexes with molecules from the surfaces of endothelial cells. Because two VEGF receptors, designated KDR and Flt, had already been discovered, he assumed that one of these complexes contained VEGF and KDR and the other consisted of VEGF and Flt. But one of the complexes had a molecular weight too low to be either—implying that it contained an entirely new VEGF receptor.



Double duty. Neuropilin is present both on neurons, where it's involved in axonal guidance, and on endothelial cells, where it aids angiogenesis.

Soker, Klagsbrun, and co-workers Seiji Takeshima, Hua Quan Miao, and Gera Neufeld set out to clone this receptor. They first made a "library" of DNA clones representing the genes active in a line of human cells that lack both KDR and Flt yet are still able to bind VEGF. They then introduced small subsets of these DNAs into cells that can't bind VEGF and looked for cells that acquired that ability. These cells had to be carrying sections of the gene encoding the VEGF-binding segment of the new receptor. Those gene segments, the group discovered, were identical to sequences from the human gene encoding neuropilin. "It was a big surprise," Klagsbrun says, "that we were dealing with a molecule that's well known in the developmental neuroscience field."

Neuropilin's role in angiogenesis seems to be different from its role in axonal guidance, however. When Semaphorin III binds to the receptor on the growing tips of neurons, it repels the cells, keeping them from getting off track. But on developing blood vessels, neuropilin seems to work in concert with KDR to stimulate vessel growth toward a VEGF source; cells to which the researchers added the genes encoding both receptors were four times more effective at binding VEGF than were cells carrying KDR alone.

Although the researchers still have a lot to do to uncover neuropilin's exact role in angiogenesis, their work so far clearly shows, says Klagsbrun, that endothelial cells have more ways of sensing and responding to navigational signals than was previously supposed. Tessier-Lavigne adds, "I certainly think it's conceivable" that blood vessel growth follows patterns similar to those governing neuronal development. He says researchers will also want to know "how much cross talk there is" between developing nerves and blood vessels, a question Klagsbrun's group is already investigating.

On the medical front, Klagsbrun has found that neuropilin is abundant on some kinds of cancer cells, suggesting that VEGF doesn't merely attract blood vessels but also feeds back on tumor cells themselves, perhaps helping them to stay alive. Developing a drug that blocks neuropilin-VEGF binding, therefore, might be a double whammy against tumors, depriving them of their survival factor while also deafening blood vessels to VEGF's siren song. And that's a benefit that Leonardo, a practical engineer as much as a perceptive artist, would have appreciated.

–Wade Roush