

Blood vessel growth in the brain relies on a protein found in tumor blood vessels

October 27 2014

Do blood vessels that feed tumors differ from other blood vessels? Fourteen years ago, experiments designed to answer that question led to the discovery of several genes that are more active in tumor-associated blood vessels than in normal blood vessels. New research now reveals the normal function of one of those genes and suggests it could be a good target for anticancer drug therapy.

A summary of the research appears in the journal *Developmental Cell* on Oct. 27.

The mystery of the gene, TEM5, began in 2000 with research conducted by Brad St. Croix, Ph.D., working in the laboratory of Bert Vogelstein, M.D., a Howard Hughes Medical Institute investigator and the Clayton Professor of Oncology, and Kenneth Kinzler, Ph.D., professor of oncology at the Johns Hopkins University School of Medicine. The researchers compared gene activity in normal [blood vessels](#) to those infiltrating colorectal tumors. Among other differences were nine genes that were highly active in the tumor-associated blood vessels, which the researchers dubbed tumor endothelial marker (TEM) 1 through 9. (Endothelial refers to the type of cell that makes up blood vessels.)

Over the ensuing decade, further experiments revealed clues regarding the function of individual TEMs. By 2010, it was known that mice missing TEM5, also known as GPR124, have defective [blood vessel growth](#) in the brain and [spinal cord](#). The mice also showed defective formation of the blood-brain barrier, the molecular "wall" crucial to

protecting the brain. These findings piqued the interest of Jeremy Nathans, M.D., Ph.D., a Howard Hughes investigator and professor of molecular biology and genetics, neuroscience, and ophthalmology at the Johns Hopkins University School of Medicine, who had been studying blood vessel growth in the eye, brain and spinal cord.

The TEM5 protein was known to be located in the outer membrane of cells, likely receiving signals from outside the cell and passing information on to a network of proteins inside the cell. But it wasn't known what signal it responds to and which protein network it connects to.

Nathans and graduate student Yulian Zhou's first clue was that the blood vessel defects in mice missing TEM5 looked similar to the defects found in mice that were missing two members of the Wnt (pronounced "Wint") family of signaling proteins, a well-known group of 19 related proteins used for communication between cells. Using cells grown in the laboratory, Zhou tested each of the 19 known Wnt proteins and found that only two of them can activate TEM5. Remarkably, they were the same two Wnt proteins previously found to play an essential role in blood vessel development in the brain and spinal cord.

To test whether TEM5 uses the "Wnt" signaling system in blood vessels, the researchers artificially activated this system specifically in [blood vessel cells](#) in mice lacking TEM5. The blood vessel defects disappeared, confirming the relationship between TEM5 and Wnt.

Nathans says that TEM5 might be a good target for cancer therapy because—although TEM5 is crucial for embryonic [blood vessel development](#)—mice do well if TEM5 is eliminated after birth. Nathans also suggests that temporarily disabling Wnt signaling in blood vessels might be used to improve drug treatment of brain diseases. Some potentially effective drugs cannot be used for treating brain diseases

because they cannot cross the blood-brain barrier. Temporarily disabling that barrier might allow these drugs to gain access to the brain.

More information: *Developmental Cell*,
[dx.doi.org/10.1016/j.devcel.2014.08.018](https://doi.org/10.1016/j.devcel.2014.08.018)

Provided by Johns Hopkins University School of Medicine

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