Why West Nile virus is more dangerous in the elderly

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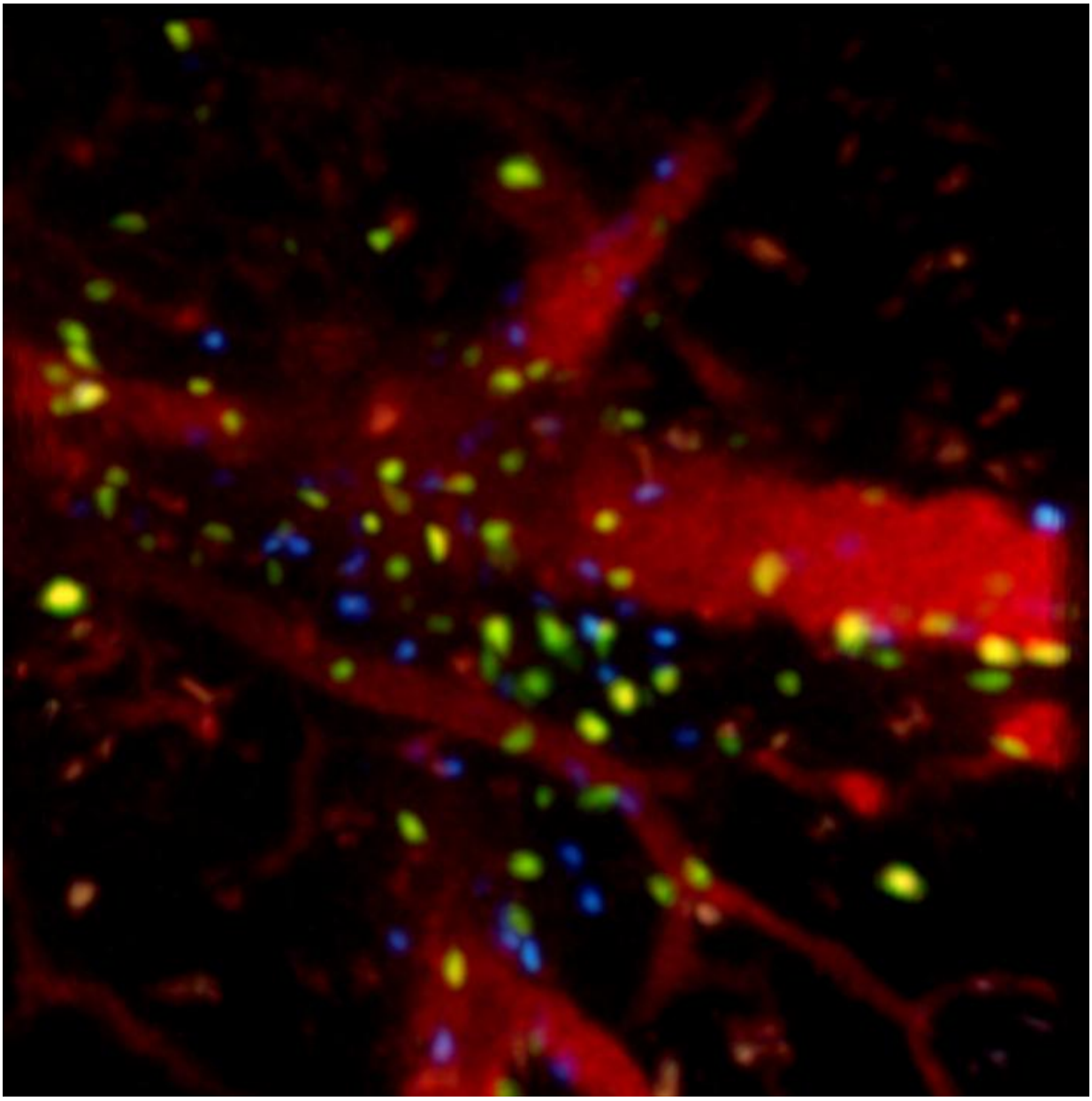

Naïve CD4+ T cells from adult (green) or old (blue) mice were transferred into recipient mice. Cellular migration was tracked in an inflamed lymph node via intravital two-photon microscopy with blood vessels labeled in red. Credit: Grzegorz Gmyrek, CC-BY

West Nile virus (WNV) is particularly dangerous in older people, who account for a large number of severe cases and deaths caused by the virus. WNV infection turns serious when the virus crosses the blood-brain-barrier and wreaks havoc among nerve cells in the brain. A study published on July 23rd in *PLOS Pathogens* suggests that several critical components of the early immune response to the virus are impaired in elderly individuals, and that this can explain their vulnerability.

Michael Diamond, from Washington University in Saint Louis, USA, and colleagues analyzed and compared the immune response to WNV infection in four-month-old (the equivalent of young adults) and 18-month-old (elderly) mice. The older mice were more than three times as likely to die after WNV infection. When the researchers measured the amount of virus present in different tissues, they found that, in addition to more virus in their blood and spleens, the older mice had 20-fold higher virus levels in their brains—which likely causes the excess deaths.

Following transmission by mosquitoes, the early specific (also called adaptive) immune response to WNV is thought to be dominated by antibodies, and, consistent with this, the researchers found that older mice had less potent WNV-specific antibody responses during the early phase of infection. They also had weaker long-term antibody memory responses.

Antibody responses are initiated in lymph nodes close to the site of

initial infection (so-called draining lymph nodes, or DLNs), where antigen-presenting cells, helper T cells, and antibody-producing B cells migrate to and interact to form so-called "germinal centers" and produce a highly specific antibody response. In the older mice, the researchers found, germinal center formation was delayed, consistent with the blunted early antibody response.

Analyzing the DLNs in more details, they found that fewer helper T cells were present, suggesting that these cells from older mice are less capable of "trafficking" to the lymph nodes. Experiments in which the researchers transplanted helper T cells from young adults or older mice into young adult recipients and then followed them by live microscopy (the paper contains several movies of these experiments) showed that this was due to reduced migratory ability of the helper T cells themselves.

Besides the reduced numbers of helper T cells in the DLNs, the researchers also found that the lymph node environment in older mice contained lower levels of immune stimulators (so-called chemokines) and therefore was less capable of attracting other immune cells necessary for germinal center formation.

While the observed differences of the individual steps were mostly modest, mathematical modeling suggested that even small delays in the trafficking of these immune cells will lead to reduced initiation of a WNV-specific antibody-response during the early stages after infection. This can lead to substantially higher early viral loads, which in turn can increase the chance of the infection spreading to the brain and worsen clinical outcome.

The authors conclude that their study "identifies a series of key early defects associated with immune responses in old animals." Regarding the mechanisms, they say "the delayed antibody and germinal center cell

responses are due to trafficking defects, which are compounded by lower levels of chemokines in the lymph node after infection. Ultimately, this leads to blunted adaptive immune responses, higher viral titers, and increased death after West Nile virus infection."

More information: *PLOS Pathogens* DOI: 10.1371/journal.ppat.1005027