Brain-immune interactions in nasal inflammation

Sanae Hasegawa-Ishii

Pathology Research Team, Faculty of Health Sciences, Kyorin University, Tokyo

Olfactory mucosa (OM) is exposed to environmental toxins, which cause nasal inflammation. Nasal inflammation may lead to rhinitis and chronic rhinosinusitis if inflammation persists. Epidemiological studies have reported that chronic nasal inflammation is associated with neuropsychiatric disorders, such as depression and anxiety. Anatomically, OM connects to the olfactory bulb (OB) via olfactory sensory neurons (OSNs) and to the subarachnoid space via the epineurium of olfactory nerves. These facts raise the possibility that nasal inflammation may perturb homeostasis of the brain and meninges. Thus, we examined whether/how acute and chronic nasal inflammation affects the OB and meninges. To induce chronic nasal inflammation, adult C57BL/6 male mice repeatedly received intranasal administration of saline or lipopolysaccharide (LPS) three times per week and were examined after 1, 2, 3, 10, 18 and 24 weeks. To analyze the recovery, mice received repeated LPS intranasal administration for 10 weeks and were kept free of additional treatment for another 10 weeks. To induce acute nasal inflammation, mice received a single intranasal administration of saline or LPS and were examined at 12, 24, 48, 72 and 96 hours and 1 and 2 weeks after administration. Within 3 weeks of repeated LPS intranasal administration, glial cells were activated, interneuron activity was reduced, and synaptic marker levels were decreased in the OB. Within 10 weeks, the OBs were atrophied particularly in their superficial layers, such as the olfactory nerve layer (ONL), glomerular layer (GL), and superficial external plexiform layer (sEPL). This shrinkage of the OB layers was not due to the death of OB cells, but to a reduction in the number and length of the axon initial segment of tufted cells. After stopping the LPS administration, the OBs recovered from the atrophy within 10 weeks. After a single intranasal administration of LPS, peripheral immune cells, mainly monocytes and neutrophils, infiltrated the OB in the ONL, GL and sEPL at 12-48 h after administration. The expression of chemokines such as CCL2 and CXCL1, which recruit monocytes and neutrophils, was increased in the OB and meninges, as revealed by real-time RT-PCR. Spectral flowcytometry analysis showed that the ratio of peripheral immune cells to whole immune cells (including microglia and macrophages) in the OB was about 6% in control mice but 36% in the LPS-treated mice at 24h. Recently, it was reported that some immune cells in the dural meninges come from the skull bone marrow and that these immune cells can move to the brain parenchyma under brain pathological conditions. Thus, skull bone marrow, meninges, and the brain parenchyma may communicate with each other in healthy and pathological conditions. We now intend to examine how this communication changes after nasal inflammation and where the peripheral immune cells that infiltrate the OB come from.