Study explains why patients with shingles feel pain

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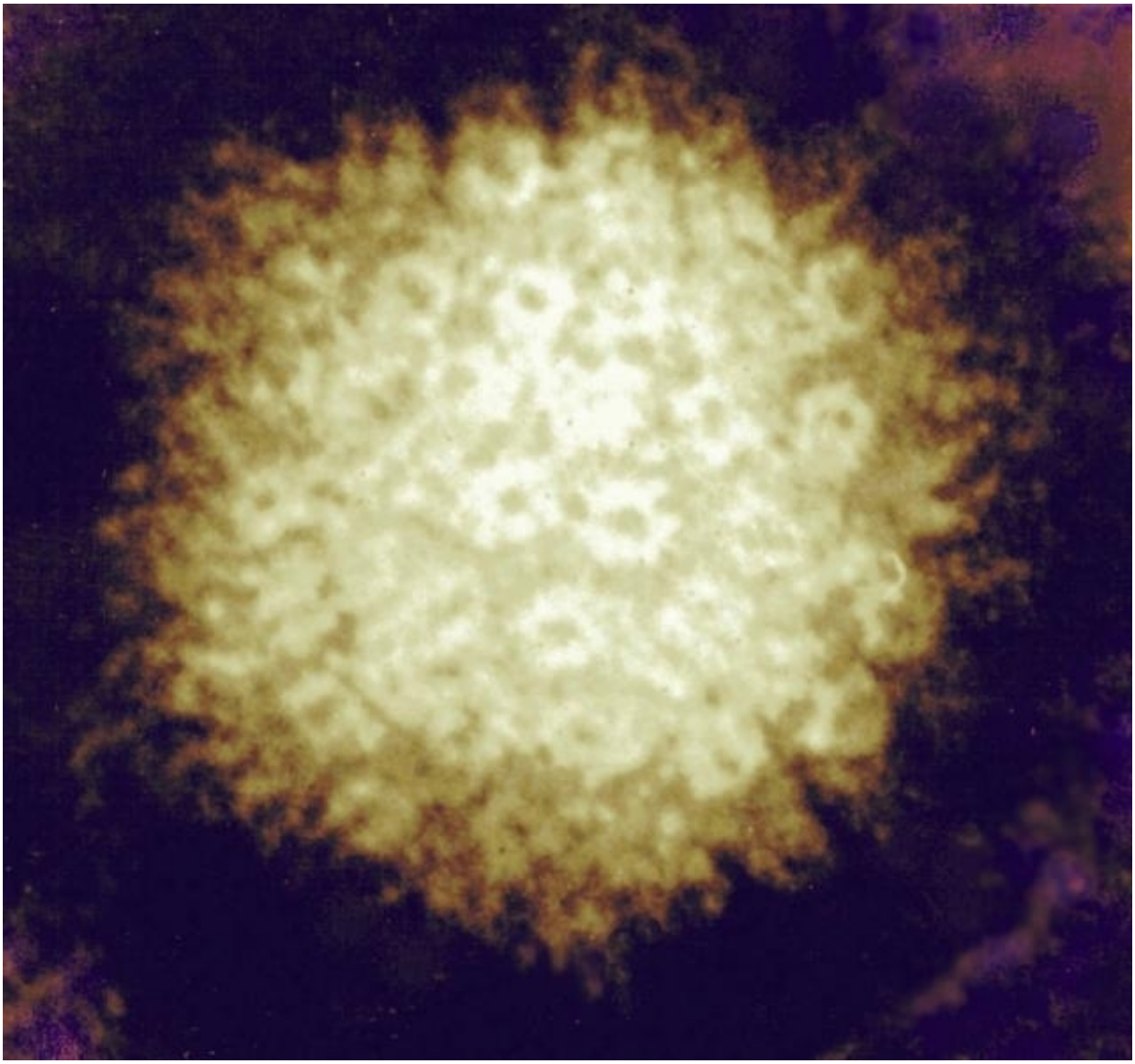

Article by researchers at the University of São Paulo published in The Journal of

Neuroscience shows role of cytokine TNF in genesis of herpetic neuralgia. Discovery could lead to novel therapeutic approaches . Credit: Varicella zoster / Wikimedia Commons

In most cases, chickenpox is a benign childhood infection with symptoms that disappear within 10 days. However, the Varicella zoster virus (VZV) that causes it remains dormant in the patient forever. In some cases, the virus can be reactivated years later, causing a different disease known as herpes zoster, or shingles.

One of the first and most unpleasant symptoms of shingles is neuralgia, or constant intense pain affecting mainly the nerves of the chest and neck, the trigeminal nerve in the face, and the lower back. The pain may be accompanied by paresthesia, a feeling of pins and needles, tingling, prickling, itching, numbness, burning and/or cold). A painful blistering skin rash often develops.

Researchers affiliated with the University of São Paulo (USP) have published a study in *The Journal of Neuroscience* describing how the immune mechanisms triggered by the reactivated virus change the way that sensory neurons work. The authors say that their discoveries lay a foundation for novel treatments not only to combat acute pain but also to prevent it from becoming chronic, a condition known as post-herpetic neuralgia.

"Treatment for herpetic neuralgia is currently based on anti-inflammatory corticosteroids, which eliminate the symptoms but can impair control of the infection because they're immunosuppressants. Some of our findings suggest that therapies capable of blocking the action of an inflammatory mediator called tumor necrosis factor (TNF) that could act more selectively and so might be more efficacious," said

Thiago Cunha, a professor at USP's Ribeirão Preto Medical School (FMRP) and co-author of the article.

Almost all adult humans carry VZV, he added. VZV usually lies dormant in the ganglia, clusters of sensory neurons that project to different parts of the body. An unexplained decrease in immunity leads to VZV reactivation in some people, causing inflammation of the ganglia. Shingles usually affects people over 60.

"Until the virus is transported along the nerves and skin lesions appear, which typically takes five to 10 days, the only symptom of shingles is neuralgia. This makes diagnosis difficult," Cunha said.

One of the contributions of this research is the validation of an animal model for studying the molecular mechanisms involved in herpetic neuralgia. Because VZV does not infect mice, the research group's experiments used herpes simplex virus type 1 (HSV-1), a related microorganism that can cause oral and genital skin lesions in humans.

"HSV-1 causes pain and skin lesions in mice, producing a condition very similar to shingles," Cunha said. "We used this model to characterize the immune mechanisms triggered by the virus in the dorsal root ganglia, which are found next to the spinal cord."

After a number of in vitro and in vivo experiments involving unmodified mice and mice that had been genetically modified not to express certain molecules that participate in immune responses or to express fluorescent tracer cells, the group formulated a theory to explain what happens in the ganglia when VZV is reactivated.

The researchers believe that immune cells, and especially macrophages and neutrophils, are attracted to the nerve tissue and begin releasing cytokines (inflammatory mediators) in an effort to eliminate the

pathogen. One of these cytokines is TNF, which binds to a protein (TNF receptor type 1, or TNFR1) on the membranes of satellite cells, the glial cells that supply potassium to surrounding neurons. TNFR1 activation by the cytokine reduces the expression of Kir4.1, a protein that acts as a channel for potassium ions to penetrate the satellite cells.

"When the neuron depolarizes [generating an electric impulse], potassium travels from the intracellular to the extracellular medium. To maintain a chemical balance at the site, the excess potassium must enter the satellite cell, and this occurs via the Kir4.1 channel," Cunha explained.

However, the group's experiments suggest that the TNF-induced decrease in Kir4.1 channel expression leads to a buildup of potassium around the neuron, which then becomes more excitable than it should be. "The neuron becomes more sensitive to any stimulus, and spontaneous pain may even occur. Thus, there are no lesions, but rather a change in the cell's functional characteristics. In our model, we evaluated the murine response to mechanical stimulus," Cunha said.

The animals' behavioral response was analyzed using the von Frey hair test, in which nylon filaments of different thicknesses are pressed against the paw. Each filament represents a force in grams and indicates the pressure tolerated without signs of discomfort.

"Whereas healthy mice in the control group began displaying discomfort when pressure reached 1 g, mice with neuralgia did so in the range of 0.04-0.08 g," Cunha said. "This demonstrates hypersensitivity. However, when we repeated the experiment and treated the mice with antibodies that neutralized TNF, they responded identically to the control group." In another experiment, mice modified so as not to express TNFR1 displayed less pain when infected by the virus than unmodified mice.

According to Thiago Cunha, data in the scientific literature show that patients who use anti-TNF medication to treat chronic inflammatory diseases such as rheumatoid arthritis are less likely to develop post-herpetic neuralgia. "This was one of the factors that led us to suspect TNF played a key role in the genesis of pain," he said. Having tested this class of drugs in the treatment of shingles, the researchers also see a possibility of investigating molecules that modulate the Kir4.1 channel.

"A drug that does this modulation indirectly, by acting on GABA B receptors, is already on the market. It's called baclofen and is mainly used as a muscle relaxant. It's an alternative worth testing," Cunha said.

More information: Jaqueline R. Silva et al. Neuroimmune–Glia Interactions in the Sensory Ganglia Account for the Development of Acute Herpetic Neuralgia, *The Journal of Neuroscience* (2017). DOI: 10.1523/JNEUROSCI.2233-16.2017

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