# Scientist identifies mechanism underlying peripheral neuropathy

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Recent research by Sandra Rieger, Ph.D., of the MDI Biological Laboratory identifying the underlying mechanisms of peripheral neuropathy, or nerve damage, has raised the prospect that drug therapies can be developed for the treatment of this condition, which causes pain, numbness and/or tingling in the hands and feet. The research was published March 28 in the *Proceedings of the National Academy of Sciences*.

Peripheral nerve damage is a common condition affecting nearly 8 million people in the United States, but until now a lack of understanding of the underlying mechanisms has held back the development of treatments. Drugs exist for the treatment of symptoms - pain relievers, for instance - but not for the condition itself, which can be caused by chemotherapy, diabetes, traumatic injury, heredity and other conditions.

"Our goal is to develop treatments that activate the repair and regeneration of damaged tissues," said Kevin Strange, Ph.D., president of the MDI Biological Laboratory. "Sandra Rieger's research has advanced that mission by elucidating a mechanism underlying peripheral neuropathy, opening the door to the development of therapeutic agents that can reverse nerve damage linked to chemotherapy, and possibly diabetes and other conditions."

The MDI Biological Laboratory, located in Bar Harbor, Maine, is an independent, nonprofit biomedical research institution focused on increasing healthy lifespan and harnessing our natural ability to repair and regenerate tissues damaged by injury or disease. The institution develops solutions to human health problems through research, education and ventures that transform discoveries into cures.

Rieger and other scientists working in the institution's Kathryn W. Davis Center for Regenerative Medicine study tissue repair, regeneration and aging in a diverse range of organisms that have robust mechanisms to repair and regenerate lost and damaged tissues.

"The general thinking is that no single drug can be effective for the treatment of all peripheral neuropathies, which stem from multiple causes," Rieger said. "But our research indicates that there may potentially be a common underlying mechanism for some neuropathies affecting the sensory nervous system that could be manipulated with drugs targeting a single enzyme."

Rieger conducted her research in zebrafish exposed to paclitaxel, a chemotherapeutic agent used for ovarian, breast, lung, pancreatic and other cancers. Paclitaxel-induced peripheral neuropathy

affects the majority of treated patients; however, those who are most severely affected (about 30 percent) have to terminate chemotherapy or reduce the dose because of this condition, which can impact cancer survival.

Rieger used zebrafish larvae to model peripheral neuropathy because the embryos develop rapidly and because the larval fish are translucent, making them ideal for studying the progression of nerve degeneration in live animals.

Rieger's research showed that paclitaxel induces the degeneration of sensory nerve endings by damaging the outer layer of the skin, or epidermis. The epidermis is innervated by free sensory nerve endings that establish direct contact with skin cells. Her research showed that degeneration is caused by perturbations in the epidermis due to an increase in matrix-metalloproteinase 13 (MMP-13), an enzyme that degrades the collagen, or "glue," between the cells. The increase in MMP-13 activity could be triggered by oxidative stress, which is also a hallmark of diabetic peripheral neuropathy.

In the research, Rieger treated the zebrafish with pharmacological agents that reduce MMP-13 activity, with the result that skin defects were improved and chemotherapy-induced nerve damage was reversed. The treatment of neuropathy with MMP-13- targeting compounds is the subject of a provisional patent filed by the MDI Biological Laboratory in January.

MMP-13 over-activation has also been linked to various other disease conditions, such as tendon injury, intestinal inflammatory and cancer, raising the possibility that drugs developed to treat peripheral neuropathy could yield other health benefits as well.

The next step is to study the effect of MMP-13 on peripheral neuropathy in mammalian models. Studies are also underway in collaboration with the Mayo Clinic in Rochester, Minn., to test the clinical relevance of these findings in humans.

**More information:** Thomas S. Lisse et al. Paclitaxel-induced epithelial damage and ectopic MMP-13 expression promotes neurotoxicity in zebrafish, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1525096113

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