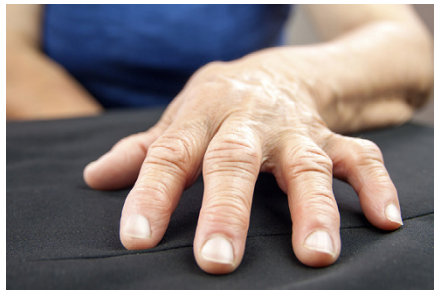
Breaking down barriers to treating rheumatoid arthritis

Rheumatoid arthritis affects up to 1.3% of people worldwide with a greater prevalence in women. It is a systemic autoimmune condition characterized by persistent inflammation of the synovial membrane that protects the joints. The most common ailments associated with rheumatoid arthritis are pain, redness and stiffness of the joints; however, the persistent inflammatory response can lead to erosion of the underlying cartilage and bone. Although there is no cure for rheumatoid arthritis, there are treatments to slow disease progression. New research by Sarah Headland at the London School of Medicine (London, UK) and colleagues has uncovered an important mechanism for preventing the erosion of cartilage that results from the immune response in joints, and this offers a potential new avenue for treating rheumatoid arthritis (*Sci. Transl. Med.* 7, 315ra190; 2015).

Treating cartilage diseases such as rheumatoid arthritis is challenging because the tissue is typically dense, avascular and impenetrable to cells. This makes the delivery of cartilage-protective agents nearly impossible. However these recent findings by Headland and colleagues show that neutrophils located in the synovial fluid surrounding cartilage secrete microvesicles that are capable of penetrating into cartilage through diffusion. Importantly, they found that when mice are unable to produce microvesicles, they develop advanced cartilage erosion. This demonstrates that microvesicle production is an important factor in maintaining healthy cartilage tissue, and manipulating the natural production of microvesicles could be a potential mechanism for treating persistent inflammation.

Many immune cell-types, such as monocytes and T-cells, produce microvesicles; however, Headland and colleagues found that it is microvesicles from neutrophils that play a key role in promoting cartilage repair. These microvesicles carry anti-inflammatory cargo that, when delivered to cartilage cells, activates the expression of genes that protect cartilage. Using a murine model of arthritis, the group injected purified microvesicles into arthritic knee tissue to test the ability of these microvesicles to



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prevent cartilage degradation. By providing arthritic mice with microvesicles that contain this anti-inflammatory payload, they were able to significantly reduce the cartilage erosion caused by the inflammatory response.

Though the presence of neutrophil-derived microvesicles in arthritic human cartilage has not been directly tested, studies have confirmed the presence of neutrophil-derived proteins. Following on these other findings, the work by Headland *et al.* could provide a new therapeutic approach for treating prolonged and persistent joint inflammation.

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VERVETS REVEAL A CAUSE OF NEURODEGENERATION

On the pacific island of Guam, some of the local Chamorro villagers exhibit a unique, endemic neurodegenerative disease known locally as Lytico-bodig and described by neuroscientists as amyotrophic lateral sclerosis-parkinsonism-dementia complex (ALS-PDC). Many characteristics of this disease resemble aspects of Amyotrophic Lateral Sclerosis, Parkinson's disease and Alzheimer's disease, and like these diseases, the cause of ALS-PDC is largely unknown.

One theory involves a neurotoxic amino acid, BMAA, that is produced by symbiotic cyanobacteria on the roots of Guamanian cycads. When ALS-PDC was most common, in the mid-twentieth century, Chamorro regularly consumed both local flour, which was made from cycad seeds, and flying foxes, which feed on the cycads and accumulate BMAA in their body fat. As flying foxes were hunted to near-extinction, the occurrence of ALS-PDC also declined to the degree that it is now considered a rare disease.

Researchers have examined different types and amounts of exposure to BMAA, but with mixed findings. Most recently, scientist Paul Cox and colleagues at the Institute for EthnoMedicine (Provo, UT) and the University of Miami Brain Endowment Bank (Miami, FL) studied how chronic dietary exposure to BMAA affected the neuropathology of vervets (*Proc. R. Soc. B* **283**, 20152397; 2015). Over a 140 day period, vervets were given fruit dosed with either a high dose of BMAA or a low dose that resembled the cumulative exposure to BMAA that a Chamorro might experience over a lifetime.

These treatments produced neuropathy in vervets that resembled that of Chamorros who died with ALS-PDC. Chronic dietary exposure to BMAA resulted in the formation of neurofibrillary tangles and β-amyloid deposits that are also found in Alzheimer's disease. As Deborah Mash, one of the study's coauthors, described in a press release, "the tangles and amyloid deposits produced were nearly identical to those found in the brain tissue of the Pacific Islanders who died from the Alzheimer's-like disease."

These findings help cement the role of BMAA in ALS-PDC, demonstrating how chronic dietary exposure can produce the neurodegenerative effects that precede this uncommon disease. This study could spur medical advances beyond the island of Guam, however, as Cox also noted that, "as far as we are aware, this is the first time researchers have been able to successfully produce [neurofibrillary] tangles and amyloid deposits in an animal model through exposure to an environmental toxin." This could provide researchers with a new model of key neuropathies that accompany and potentially cause many neurodegenerative conditions, including Alzheimer's disease.

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