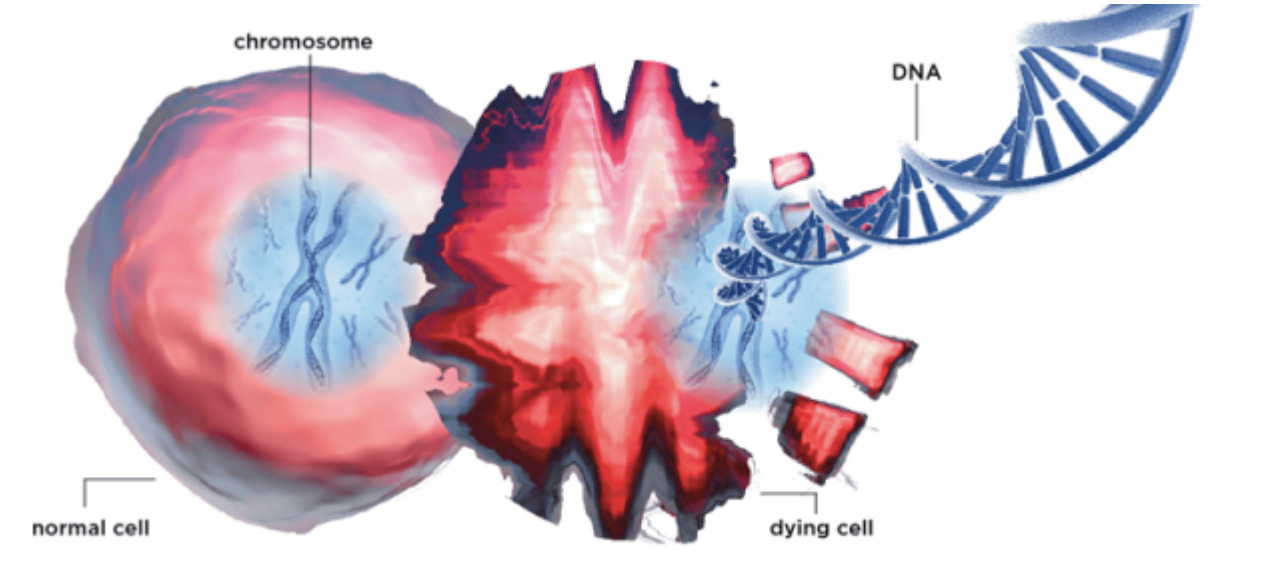
Finding biomarkers of MS

Compounds in the blood and spinal fluid may help to identify MS earlier and determine the most effective treatments.

by Mary E. King, PhD

Wouldn't it be helpful to have a single, individualized test that could tell people very early on whether and what type of multiple sclerosis they have, as well as how quickly or severely the disease may progress without treatment, and whether a disease-modifying treatment is helping? As it turns out, such a test may be in the works.

Researchers previously identified a few biomarkers—measurable substances in the body that signal the presence of a specific condition or disease—that show up in the blood and spinal fluid of people with MS. The lesions seen on MRI are also considered biomarkers, but these typically don't appear until after the disease
has already caused some damage.



Researchers are looking to identify biomarkers—measurable substances in the body that can signal the presence of MS and determine appropriate treatments. One team of researchers is focusing on finding unique "signatures" in DNA that are released from cells when they are badly damaged or dying, which could serve as biomarkers for damaged neurons in MS.

In fact, each of the biomarkers currently available for clinical use is limited in how much detail it can provide and the circumstances in which it is useful. That's one reason why MS researchers are keen to find additional compounds—or a pattern of compounds—that will provide a much broader spectrum of personalized information, explains Mark Allegretta, PhD, a cell biologist and commercial development specialist who leads the National MS Society's Fast Forward commercial research programs. The following studies represent just a handful of the current Society-funded work in this area.

Marking the loss of brain cells

Eitan Akirav, PhD, lead scientist and assistant professor of research at the Winthrop University Hospital in Mineola, New York, is focusing on finding DNA that is released from cells. (DNA is the material in each cell that carries genetic information, including all of the recipes for producing the proteins that we need.) Cells release DNA when they are badly damaged or dying, so this DNA could serve as a biomarker for damage to neurons caused by MS.

Dr. Akirav explains that as part of their normal activity, our cells attach a small piece of a molecule, called a methyl group, to many specific locations on the DNA to create unique DNA "signatures." These signatures (known as "methylation patterns") are what tell each cell which proteins it should produce.

Dr. Akirav, together with Dr. Mark Stecker from Winthrop's department of neurology, is looking for a marker of brain cell injury that will specifically indicate the presence of MS. They hope to find a unique DNA signature released into blood from damaged or dying neurons and

from oligodendrocytes (cells that make myelin). That information, they believe, not only will help to identify MS in the first place, but also may better diagnose subtypes of MS—ahead of the traditional method of watching for symptoms of MS.

The ability to identify DNA from dying cells in the blood of people with MS would be an exciting result. It would mean this biomarker could be measured with a simple blood test, rather than requiring a spinal tap or expensive imaging procedures.

“We have very exciting preliminary data showing that we can detect a type of methylated DNA in the blood of people with relapsing-remitting MS,” which is not present in the blood of those without MS or people with disease remission,Dr. Akirav says. He hopes that measuring changes in this DNA will also be useful for assessing individuals’ responses to therapy and, possibly, for predicting the severity of their disease. He readily acknowledges, however, that it is too soon to apply his findings to the clinical setting. Recently, Dr. Akirav’s team was awarded a research grant from the Marilyn Hilton Foundation to further extend his findings to the more challenging progressive forms of MS.

Identifying changes in DNA

Nancy Monson, PhD, associate professor of neurology and neurotherapeutics, and associate professor of immunology at the University of Texas Southwestern Medical Center in Dallas, is taking a different approach, looking at broad changes in the DNA of B cells, a type of white blood cell that makes antibodies. Antibodies are proteins that normally bind to infectious agents like bacteria and help clear them from the body. “What we think is happening in MS is that maverick B cells are making antibodies that target the brain instead,” she explains.

Dr. Monson’s study compared the DNA recipes for antibodies from B cells in the spinal fluid from three types of individuals: people with MS, people with other neurologic diseases and people without a known condition. “It turns out that people with MS make a different set of DNA recipes for antibodies—one that we don’t find in people who don’t have MS or in people with other neurologic diseases,” she states. So far, in preliminary data, the approach has been 94 percent accurate in identifying individuals with MS.

Using this information to develop a test for B cell DNA recipes that are only found in MS may help clinicians identify disease early. The hope is that timely treatment will slow or prevent disease progression. To that end, Dr. Monson’s laboratory is collaborating with DioGenix Inc. (which recently merged into Amarantus Diagnostics), in partnership with the National MS Society, to see if that same antibody DNA can also be found in the blood, which would eliminate the need for a spinal tap. It is too early to know when the study will net results.

A single protein in spinal fluid

Dr. Gavin Giovannoni, the chair of neurology at the Blizard Institute at Barts and The London School of Medicine and Dentistry, is investigating whether the amount of a specific protein, called neurofilament (NF) protein, measured in spinal fluid will indicate how well MS therapies are working to prevent the destruction of nerve fibers.

“NF is released into the spinal fluid in conditions that cause nerve damage, including MS,” Dr. Giovannoni explains. However, blood does not appear to be a good alternative for spinal fluid when measuring this particular biomarker, he adds.

In a pilot study, Dr. Giovannoni and his team are comparing changes in the concentrations of NF in the spinal fluid of 60 people with early secondary-progressive MS who are participating in a clinical trial comparing standard therapy for MS with a combination of standard therapy and a potential new treatment. “We think that in the future we will be able to analyze NF levels to make decisions about treatments. If someone has a high level of NF while on a given therapeutic regimen, this may indicate ongoing damage and the need to escalate therapy,” he says. Results are expected toward the end of 2016.

Discovering a pattern of differences

Charlotte Teunissen, PhD, head of the neurochemistry laboratory and biobank in the department of clinical chemistry, and associate professor at VU University Medical Center, Amsterdam, The Netherlands, is trying to identify a way to distinguish relapsing-remitting MS from primary-progressive MS early on in the disease process. She explains, “Having reliable biomarkers [for the two types of MS] may offer clues to the underlying causes of MS progression” that could help identify targets for new treatment options.

Funding from the International Progressive MS Alliance is enabling her team to apply advanced technology to identify differences in the types and amounts of many proteins at once, including many inflammatory and brain-specific proteins. “It’s like providing a unique fingerprint,” Dr. Teunissen says, adding that “the beauty [of this approach] is that we may find [differences in] unexpected proteins, so we are not bound to current knowledge or hypotheses of MS.” She expects results in late 2015.

Future research in biomarkers

The National MS Society continues to encourage more research on biomarkers. As Dr. Allegretta points out, “We need a more reliable way to diagnose MS earlier in its course, and beyond that, to provide individuals with a personalized approach, identifying in advance which treatments will provide that person with the best response to therapy.”

Mary E. King, PhD, is a freelance medical writer in Boulder, Colorado.

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