EDITORIAL

A Metabolic Vulnerability of Vision

Henna Tyynismaa, Ph.D.

New therapies targeting metabolic vulnerabilities of specific tumor types have created wide interest in recent years. Through research now reported in the *Journal* by Gantner et al.,[1] metabolic precision therapy may become possible in patients with a rare eye disease, macular telangiectasia type 2, which leads to a progressive loss of central vision in both eyes in middle-aged or older persons.[2]

The macula is the small area in the back of the eye that is responsible for high-resolution (i.e., sharp) vision. In the center of the macula is the fovea, which has the highest density of cone photoreceptor cells and thus, as compared with other parts of the macula, provides the highest degree of visual resolution. In persons with macular telangiectasia type 2, foveal photoreceptors degenerate, preventing the transduction of light signals to the brain. Telangiectasia refers to small dilated blood vessels, which are secondary abnormalities in this primarily neurodegenerative condition. There is currently no effective treatment for the condition, although encouraging results from a phase 2 trial of a neuroprotective agent, ciliary neurotrophic factor, were reported earlier this year,[3] and an anti–vascular endothelial growth factor drug, bevacizumab, has been found to ameliorate secondary blood-vessel formation.[4]

A genetic component of macular telangiectasia type 2 was suspected, but the combination of genetic heterogeneity and environmental factors affecting the penetrance of genetic effect has made it challenging to establish clear inheritance patterns and to identify disease genes. A genomewide association study in combination with the analysis of blood metabolites from patients with macular telangiectasia type 2 provided some evidence to support involvement of the serine biosynthesis pathway in conferring susceptibility to the disease.[5] Gantner et al. now report on specific genetic causes of macular telangiectasia type 2: variants in the genes *SPTLC1* and *SPTLC2*, the protein products of which participate in sphingolipid metabolism. (Sphingolipids are a large family of lipids that among other roles, mediate a variety of metabolic, growth, and cell-survival processes.)

It was previously established that pathogenic variation in *SPTLC1* and *SPTLC2* causes another neurodegenerative disease, hereditary sensory and autonomic neuropathy type 1 (HSAN1), which affects the peripheral nerves and causes sensory abnormalities such as blunted nociception and variable limb weakness.[6,7] Both genes are needed to make the key enzyme in sphingolipid synthesis, serine palmitoyltransferase (SPT). The etiologic mutations in *SPTLC1* and *SPTLC2* do not reduce the activity of SPT but instead alter its substrate specificity from serine to alanine. This alteration results in the production and accumulation of deoxysphingolipids,[8] which are neurotoxic.

Having obtained earlier evidence of possible disruption of serine metabolism in persons with macular telangiectasia type 2, with *SPTLC1* and *SPTLC2* as strong candidate genes, the authors carefully examined 11 patients with HSAN1 for macular telangiectasia type 2–associated macular changes and found such changes in 9 of the patients. Further studies in larger patient cohorts are needed to establish how commonly macular telangiectasia type 2 and sensory neuropathy co-occur. Is macular degeneration typical of all or

only specific mutation types? Do any patients with macular telangiectasia type 2 who do not have *SPTLC1* or *SPTLC2* mutations have neuropathic symptoms? What other monogenic causes (if any) in the same pathway might contribute to macular telangiectasia type 2? Why sensory neurons and foveal photoreceptors are especially vulnerable to elevated levels of deoxysphingolipids is another unanswered question, although a recent study provides a potential clue: the accrual of a specific type of deoxysphingolipid in the mitochondria promotes mitochondrial fission and glucose intolerance.[9] This, in turn, may preferentially compromise the function of cells with high energy requirements, such as neurons (the photoreceptor is a type of neuron).

Gantner et al. went on to analyze 125 persons with macular telangiectasia type 2 who did not test positive for mutations affecting SPT. (As an aside, it seems from the comparatively large size of this group of patients that such mutations cause macular telangiectasia type 2 in a minority of affected persons). However, even in the absence of an *SPTLC* mutation, aberrant serine metabolism nonetheless appears to have a role in the pathogenesis of disease, because low serine and high deoxysphingolipid levels were found in the blood of the 125 patients with macular telangiectasia type 2 who did not have *SPTLC1* or *SPTLC2* mutations. The authors suggest that the low serine levels increase deoxysphingolipid levels by reducing substrate availability for SPT as a general mechanism. Testing of a serine-depleted diet in mice supported these findings: elevated levels of deoxysphingolipids developed in the mice, along with retinal and peripheral sensory deficits. Using human retinal organoids, the authors showed that deoxydihydroceramides, derivatives of deoxysphingolipids, are toxic to photoreceptors. Inhibition of ceramide synthesis or treatment with fenofibrate to stimulate deoxysphingolipid degradation prevented death of the photoreceptor cells.

Serine supplementation has been shown to reduce levels of deoxysphingolipids in humans.[10,11] The results of a randomized, placebo-controlled trial of high-dose serine (400 mg per kilogram of body weight per day) to treat persons with HSAN1 were, without sensitive biomarkers of disease progression, difficult to interpret.[12] The serine–sphingolipid pathway now represents a target for experimental strategies in the treatment of macular telangiectasia type 2, but as the authors rightly caution, it would be premature to prescribe serine or fenofibrate without a better understanding of disease etiology within the broader patient population. In the meantime, patients with HSAN1 should be evaluated for signs of macular telangiectasia type 2, and vice versa.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Stem Cells and Metabolism Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland.

This editorial was published on September 11, 2019, at NEJM.org.

1. Gantner ML, Eade K, Wallace M, et al. Serine and lipid metabolism in macular disease and peripheral neuropathy. N Engl J Med. DOI: 10.1056/NEJMoa1815111
2. Charbel Issa P, Gillies MC, Chew EY, et al. Macular telangiectasia type 2. Prog Retin Eye Res 2013;34:49-77.
3. Chew EY, Clemons TE, Jaffe GJ, et al. Effect of ciliary neurotrophic factor on retinal neurodegeneration in patients with macular telangiectasia type 2: a randomized clinical trial. Ophthalmology 2019;126:540-9.
4. Roller AB, Folk JC, Patel NM, et al. Intravitreal bevacizumab for treatment of proliferative and nonproliferative type 2 idiopathic macular telangiectasia. Retina 2011;31:1848-55.
5. Scerri TS, Quaglieri A, Cai C, et al. Genome-wide analyses identify common variants associated with macular telangiectasia type 2. Nat Genet 2017;49:559-67.
6. Dawkins JL, Hulme DJ, Brahmbhatt SB, Auer-Grumbach M, Nicholson GA. Mutations in SPTLC1, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. Nat Genet 2001;27:309-12.
7. Rotthier A, Auer-Grumbach M, Janssens K, et al. Mutations in the SPTLC2 subunit of serine palmitoyltransferase cause hereditary sensory and autonomic neuropathy type I. Am J Hum Genet 2010;87:513-22.
8. Penno A, Reilly MM, Houlden H, et al. Hereditary sensory neuropathy type 1 is caused by the accumulation of two neurotoxic sphingolipids. J Biol Chem 2010;285:11178-87.
9. Chaurasia B, Tippetts TS, Mayoral Monibas R, et al. Targeting a ceramide double bond improves insulin resistance and hepatic steatosis. Science 2019;365:386-92.
10. Auranen M, Toppila J, Suriyanarayanan S, et al. Clinical and metabolic consequences of L-serine supplementation in hereditary sensory and autonomic neuropathy type 1C. Cold Spring Harb Mol Case Stud 2017;3(6):a002212.
11. Garofalo K, Penno A, Schmidt BP, et al. Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. J Clin Invest 2011;121:4735-45.
12. Fridman V, Suriyanarayanan S, Novak P, et al. Randomized trial of l-serine in patients with hereditary sensory and autonomic neuropathy type 1. Neurology 2019;92(4):e359-e370.

DOI: 10.1056/NEJMe1910322