structures and to establish linkages between migrating populations (*7*). Finally, isotope-ratio mass spectrometry is sufficiently advanced that automated accessible analyses are available at relatively low cost. There is, however, an urgent need to standardize stable isotope data among laboratories. Despite these technological growing pains, we can soon expect intriguing breakthroughs in our understanding of the global migrations of animal species ranging from migratory bats and songbirds to butterflies.

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PERSPECTIVES: BIOMEDICINE

Under Pressure

James S. Friedman and Michael A. Walter

Sight is possibly the most valued of the five senses. The loss of vision through disease affects countless millions worldwide and will become an increasing problem as the global population ages. One common cause of sight loss is glaucoma, a disease characterized by the gradual loss of peripheral vision (see the figure). It is predicted that at least 66 million people worldwide have glaucoma, and that this disease leads to bilateral blindness in more than 6 million individuals (*1*). Glaucoma is the principal cause of blindness among African Americans and the second leading cause of blindness among Caucasians. On page 1077 of this issue, Sarfarazi, Rezaie, and their colleagues (*2*) show that mutations in the *OPTN* gene, which encodes the optineurin protein, are responsible for a significant proportion of cases of primary open-angle glaucoma, the most common form of this disease.

The Sarfarazi laboratory has an impressive track record in the field of glaucoma genetics. This group was the first to map and isolate *CYP1B1*, the gene mutated in about 85% of congenital glaucoma patients (*3, 4*). In their new study, Rezaie *et al.* (*2*) applied genetic linkage analysis to members of a single family (pedigree) in whom glaucoma segregated as an autosomal dominant trait with the GLC1E locus on chromosome 10p14–p15 (*5*). After reducing the GLC1E critical region to a length of 5 cM and excluding four other genes, the authors selected *OPTN* as their candidate gene. They found that in members of this large glaucoma pedigree the *OPTN* gene contained a missense mutation that resulted in a $Glu^{50} \rightarrow$ Lys (E50K) amino acid change in the optineurin protein. A broader search of 54 additional adult-onset glaucoma families with normal to moderately elevated eye pressure (which can be a predictor of glaucoma) uncovered several additional *OPTN* mutations. Some of these families carried the E50K mutation, one family carried an insertion in *OPTN* resulting in a premature stop codon, and one family had an $Arg^{545} \rightarrow$ Gln residue change. A "risk-associated" $Met^{98} \rightarrow$ Lys change was present in 12.1% of individuals without a family history of glaucoma and in 17.8% of their kindreds with glaucoma. The high frequency of the E50K mutation in glaucoma patients was statistically significant, even though the risk-associated amino acid change is present in the normal population at a frequency of about 2%.

Rezaie *et al.* (*2*) detected expression of *OPTN* mRNA and protein in the tissues of healthy individuals. With Northern blot analysis, they found *OPTN* mRNA expression in the trabecular meshwork and nonpigmented ciliary epithelium of the human eye. In addition, human optineurin is expressed in retina epithelial cells, fibroblasts, skeletal muscle, and kidney. Immunoblotting experiments revealed that optineurin is present in the aqueous humor (the liquid in the anterior chamber of the eye) of a variety of species. Immunocytochemistry confirmed that optineurin is a secreted protein localized in the Golgi apparatus of cells. Cultured dermal fibroblasts derived from a patient with an E50K missense mutation in *OPTN* produced less optineurin than fibroblasts from a healthy control. This suggests that loss of one allele of the *OPTN* gene through mutation (haploinsufficiency) could be the underlying cause of glaucoma. The biochemical and molecular analysis by Rezaie *et al.*, coupled with their genetic data, clearly shows that mutations in *OPTN* are responsible for many cases of adult-onset primary open-angle glaucoma.

Tunnel vision. "Self-Portrait with Bandaged Ear" by Vincent van Gogh as seen by an individual with normal vision (**top**) and by a patient with peripheral vision loss associated with the early stages of glaucoma (**bottom**).

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Six loci potentially harboring genes involved in this form of glaucoma have been mapped, but, so far, only one other candidate gene, *TIGR/MYOC*, has been identified (*6*). Mutations in *TIGR/MYOC* are present in about 4% of familial primary open-angle glaucoma cases. Among primary open-angle glaucoma patients, 16.7% of low- to moderate-tension glaucoma families carry *OPTN* mutations (*6*). This finding confirms that mutations in the *OPTN* gene are involved in a significant proportion of primary open-angle glaucoma cases. Examining patients with high- and low-pressure forms of this disease will allow the frequency of *OPTN* mutations to be determined.

The Rezaie *et al.* study delivers the gift of a new protein to researchers working to understand glaucoma pathogenesis and to find therapeutic interventions for treating this blinding disease. Optineurin is known to interact with several important proteins including huntingtin, the protein mutated in a neurodegenerative disease called Huntington's (*7*). In addition, optineurin may be a component of the tumor necrosis factor–α signaling pathway, which regulates programmed cell death (*8*). Rezaie and coworkers speculate that optineurin's normal protective task in this pathway may be disrupted in glaucoma patients carrying *OPTN* mutations. Interestingly, *TIGR/MYOC* may also be part of a neuroprotective response (*9*). The identification of more genes implicated in glaucoma increases the possibility that we may elucidate a common pathway that is disrupted in different forms of this disease. Recently, work by Vincent *et al.* uncovered a potential modifying effect of the *CYP1B1* gene on *TIGR/MYOC* (*10*). Individuals with

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mutations in both genes developed glaucoma at a much younger age than did family members with mutations in *TIGR/MYOC* alone. This is consistent with the notion that certain genes mutated in glaucoma patients can themselves modify the expression of other glaucoma genes. Further research is required to determine whether *OPTN* is a modifier gene or whether it is modified by other glaucoma genes. The important contribution made by Rezaie *et al.* will assist in the early detection of primary open-angle glaucoma. Additionally, the new work will help researchers to establish treatments for those affected with this blinding and debilitating condition.

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PERSPECTIVES: TRANSCRIPTION

Mediator Meets Morpheus

Michael Meisterernst

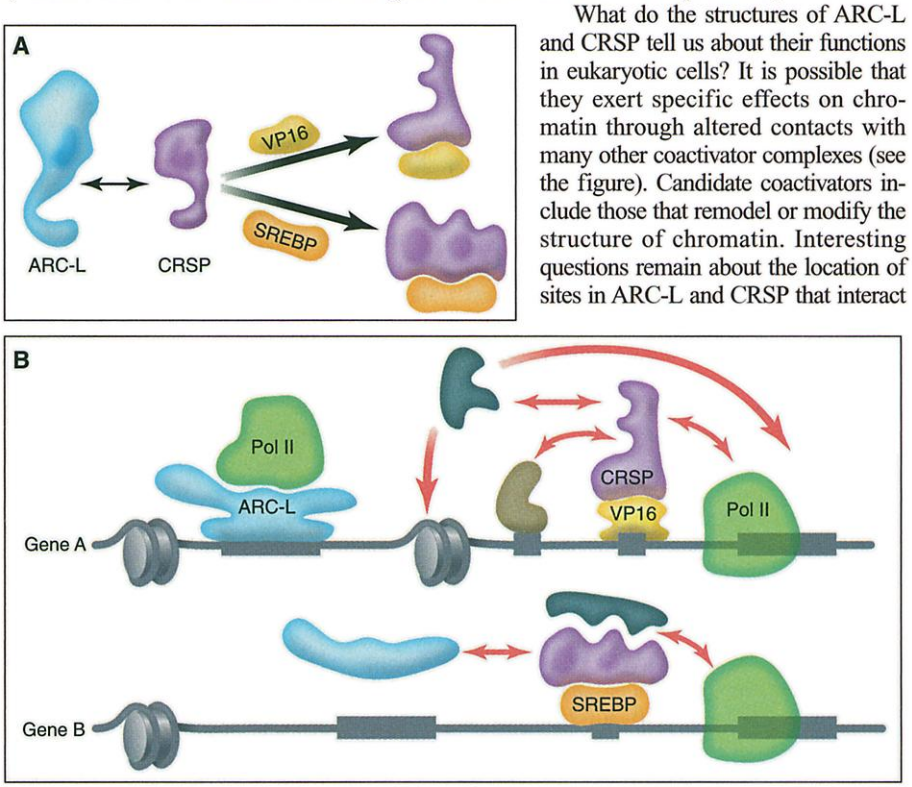
In eukaryotic cells, the transcription of genes into mRNAs is characterized by an unrivaled wealth of protein coactivator complexes that regulate the enzyme responsible for transcription, RNA polymerase II. A central player in the transcriptional machinery is the large coactivator complex Mediator, first characterized in yeast (*1*). Similar to yeast Mediator are related human coactivator complexes that help to switch on transcription by binding to activators and to RNA polymerase II itself (*2*). On page 1058 of this issue, Taatjes *et al.* (*3*) report the structure of two of these Mediator-like coactivator complexes, ARC-L and CRSP. With electron microscopy, they demonstrate that the structures of ARC-L and CRSP are not rigid but rather exhibit a high degree of conformational flexibility, which depends unexpectedly on the particular activators to which they are bound. In elegant biochemical studies, the authors show that CRSP is transcriptionally active but ARC-L is not, and that CRSP may control transcription by changing its conformation.

Mediator activities were first identified in the early 1990s in both yeast and mammalian cells (*2*). The large human coactivator complexes (TRAP and DRIP) were isolated and purified only several years later, using affinity columns composed of the thyroid hormone receptor and vitamin D receptor. In eukaryotic cells, a number of coactivators and corepressors of transcription including ARC, NAT, SMCC, CRSP, and PC2 (*4*–*7*) were found to be similar to the Mediator complex in yeast (*2*). Yeast Mediator and its eukaryotic relatives are coactivators that bind to various transcriptional activators, yet they also modulate the basal activity of RNA polymerase II (*8*).

Taatjes *et al.* describe the complete purification and characterization of CRSP and ARC-L and delineate their interactions with various activators of transcription. Given that both of these complexes have molecular weights in the megadalton range, electron microscopy is the only method currently available with which to visualize their structure. ARC-L and CRSP share many of the same subunits, although the ARC-L complex is much larger. Electron microscopy can provide insights into the global conformation of these complexes, the arrangement of their subunits, and contact sites for coactivator partners. So far, electron microscopy has successfully elucidated the structure of a large transcription factor complex, TFIID (which binds to the TATA boxes in gene promoters), and the interaction of yeast Mediator with RNA polymerase II (*9*–*11*).

Given the difficulties in obtaining sufficient purified material, solving the structures of ARC-L and CRSP is a formidable task. Surprisingly, CRSP undergoes dramatic conformational changes when it binds to activators of transcription. Among these activators are herpes simplex viral protein VP16 and the sterol response element binding protein, SREBP, which contact different regions of Mediator-like complexes, inducing long-range conformational changes in them. When bound to these activators, CRSP appears to be extended, not globular in structure, somewhat resembling the extended shapes generated when molten lead is poured onto cold water (a New Year's Eve tradition in Germany that supposedly enables the future to be predicted).

What do the structures of ARC-L and CRSP tell us about their functions in eukaryotic cells? It is possible that they exert specific effects on chromatin through altered contacts with many other coactivator complexes (see the figure). Candidate coactivators include those that remodel or modify the structure of chromatin. Interesting questions remain about the location of sites in ARC-L and CRSP that interact



CRSP control of transcription. (**A**) The large and small Mediator-like coactivator complexes, ARC-L and CRSP, have distinct structures. Activators of transcription, such as VP16 and SREBP, modulate the structure of CRSP, altering its conformation. (**B**) The altered conformation of CRSP may influence its interactions with other coactivators (arrows) or may alter its activity. The transcriptionally inactive ARC-L could serve as a docking site for RNA polymerase II (which usually is not limiting under in vitro conditions) or may exert a negative effect on transcription by competing with CRSP for transcriptional activators or other coactivator complexes.

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