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

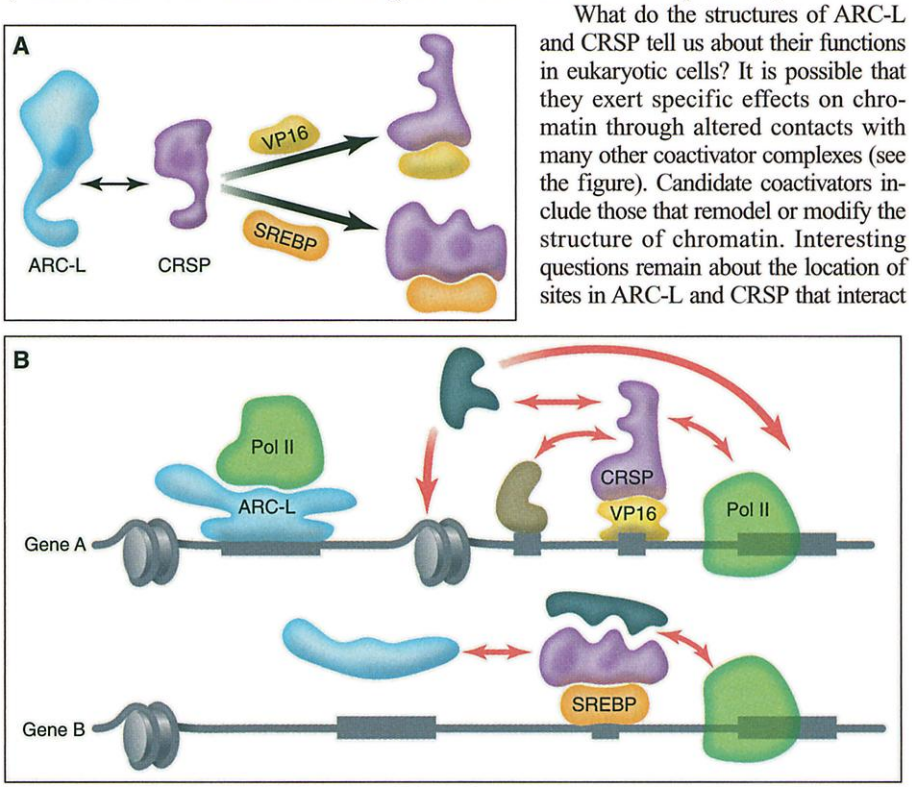
In eukaryotic cells, the transcription of genes into mRNAs is characterized by an unrivaled wealth of protein coactivator complexes that regulate the enzyme responsible for transcription, RNA polymerase II. A central player in the transcriptional machinery is the large coactivator complex Mediator, first 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.

The author is in the Gene Expression Department, National Research Center for Environment and Health–GSF Institute of Molecular Immunology, Marchionini-Strasse 25, D-81377 Munich, Germany.

with RNA polymerase II. Analysis of yeast Mediator bound to RNA polymerase II reveals intimate contacts between the two complexes, with RNA polymerase II in a globular conformation and Mediator covering it like a hat (*11*). Intriguingly, the carboxyl-terminal domain of RNA polymerase II induces a conformation in CRSP resembling that of CRSP-VP16 (*12*), suggesting a related effect of RNA polymerase II and VP16 on transcription. Moreover, despite their different structures, CRSP-VP16 and CRSP-SREBP performed identically in the Taatjes *et al.* transcription assay. Thus, the structures of ARC-L and CRSP do not disclose precise molecular downstream pathways. In addition, no data exist about the influence of the rest of the transcriptional machinery on the conformations of ARC-L and CRSP. It is also unclear whether ARC-L is a negative regulator of transcription like NAT (*12*) or a positive regulator that provides a docking site for RNA polymerase II (see the figure). Importantly, the new work suggests an unexpected level of specificity in transcriptional control that is established through conformational differences in Mediator-like complexes induced by activators. This points to versatile ways in which these cofactor complexes could exert effects on chromatin and on transcriptional activity.

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PERSPECTIVES: GEOCHEMISTRY

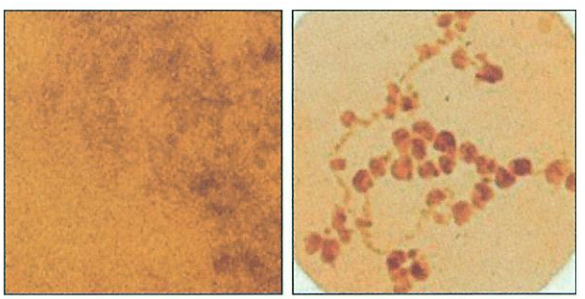
The Fate of Chlorine in Soils

W. H. Casey

The Irish noun "leannán" has two definitions: a lover or sweetheart and a chronic irritating affliction (*1*). Geochemists could use such a word to describe the degradation products of natural organic matter. These products are complicated polyelectrolyte macromolecules called humic and fulvic acids that control much of the reactivity of soil, including its fertility. Yet they also bind and disperse toxic metals such as plutonium in natural waters. Furthermore, large humic acids contain hydrophobic regions that dissolve aromatic organic compounds such as organohalogen pesticides, which are normally insoluble in water. They are thus key vectors for dispersing contaminants throughout natural waters.

Despite their obvious importance, little is known about humic and fulvic acids. They have no fixed stoichiometry or structure, cannot be crystallized, and are famously difficult to characterize reproducibly. In recent years, brilliant x-ray sources, in situ imaging methods, and nuclear magnetic resonance spectroscopies have begun to shed some light on their properties. On page 1039 of this issue, Myneni (*2*) elucidates their interaction with chlorine.

In 1999, Myneni *et al.* (*3*) used an x-ray microscope to provide the first in situ images of the macromolecules in various solutions and soils (see the figure). They showed how the molecules coil and relax depending on the composition of the solution and their proximity to a mineral surface. Myneni (*2*) now uses another synchrotron method to document changes in the chemical state of chlorine in humic materials and in leaf litter in soil throughout the year. He confirms the startling conclusion (*4*, *5*) that organochlorine compounds are common in soil and that there is a net transfer of chlorine from inorganic to organic forms with weathering. This stunning result has important social and scientific implications.



Fluvial fulvic acid in uncoiled (left) and coiled form (right) (*3*). The average sizes of globular coils are on the order of 300 nm^3.

Myneni's real breakthrough is the application of a simple, elegant, and nondestructive method to follow the reactions. Previous workers used extraction methods to show chlorination of aromatic moieities in soil, but their techniques were usually indirect and tedious. Myneni uses the position of the x-ray absorption edge for chlorine in the bulk soil or organic debris. This position is sensitive to the electronic structure and molecular environment of chlorine without extensive sample preparation. Applied to leaf litter, it records an evolution from inorganic chloride ion (Cl^-), which dominates in fresh leaves, to chlorinated hydrocarbons and aromatic products in decomposed (humified) material in soils.

The chlorination of aromatic organics by hydrogen peroxide is thermodynamically favored (*6*) but kinetically impeded. Myneni's results indicate that an abundant catalytic peroxidase facilitates this reaction in soils, as has been suspected (*4*, *5*). The results, when considered along with those of previous workers, clearly show that chlorination of organic compounds in humic materials is widespread and may account for the puzzling organochlorine concentrations found in unpolluted environments.

Myneni's results are not perfect. Because he cannot derive a mass balance for chlorine from the spectra, it remains unclear whether the organic molecules are really progressively chlorinated during humification or whether the signal from the chloride ion is simply reduced with time by aqueous leaching of the chloride ion from the plant material so that the relatively insoluble organochlorines, either natural or anthropogenic, become more conspicuous with time. This issue has been addressed before (*4*, *5*) and will be worked out soon by coupling x-ray spectrometry to traditional bulk methods of analysis.

The importance of understanding these reactions cannot be overstated. Halogenated organics are ubiquitous in our lives and are usually used to our benefit. Even DDT is still used in acutely malarious countries to reduce infant mortality (*7*), and it would be monstrous to deny populations use of a chlorinated pesticide without providing an effective replacement. Evident too, however, are the considerable environmental dangers of some of these compounds (*8*).

In his exceptionally well-researched polemic against organochlorine molecules and the chlorine industry, Thornton (*9*) argues that anthropogenic organochlorine compounds should be banned outright because of their deleterious effects to health and because of their dispersion and persistence in the environment. Thornton's

The author is in the Department of Land, Air and Water Resources and the Department of Geology, University of California, Davis, CA 95616, USA. E-mail: whcasey@ucdavis.edu