cognitive capacities affect the process of language development. For instance, auditory short-term memory is an area of particular strength in WS, and an area of particular weakness in both Down syndrome and SLI. Klein and Mervis (*3*) suggested that children with WS do best on language tests that involve memory, and others (*5*) have noted that within a WS sample, language level is closely linked to auditory short-term memory. This suggests that one important factor determining language proficiency in different clinical groups could be the capacity for auditory short-term memory. This idea meshes well with the proposal that a specialized system for remembering speech evolved in humans as a prerequisite for learning language (*6*).

The newborn brain is not a homogeneous mass. Differentiation of sensory areas is established early, and some parts of the brain are implicated in language learning more than others. It is not surprising that genetic disorders affecting the brain can yield characteristic behavioral phenotypes. We must beware, however, of jumping to the conclusion that different language profiles reflect the status of specialized innate brain areas that mediate complex functions such as syntax. Different profiles could reflect the status of, for example, simple auditory memory. To understand just how this might occur, we need to study the process of development in genetic disorders, as well as its final outcome. The Paterson study has made a promising start, and its findings suggest that our assumptions about developmental disorders may be radically challenged by tracing cognitive development from its earliest manifestations.

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PERSPECTIVES: MOLECULAR BIOLOGY

Mutant Dyskerin Ends Relationship with Telomerase

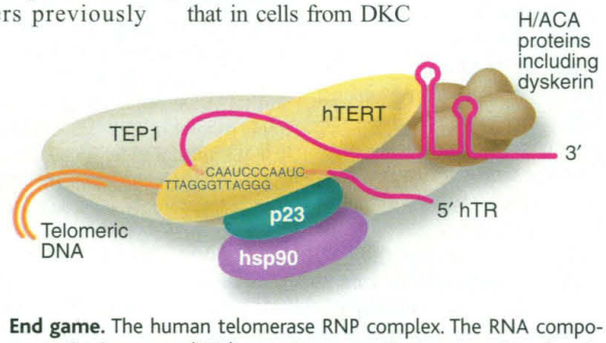
Jerry W. Shay and Woodring E. Wright

Dyskeratosis congenita (DKC) is a rare inherited disorder that is characterized by early death from bone marrow failure or pulmonary complications (*1*). Other symptoms include fragile bones, the absence of hair, progressive nail dystrophy, darkening or absence of skin color, underdeveloped testes, precancerous cells in mucous membranes, abnormalities of the gastrointestinal tract, pulmonary fibrosis, and an increased risk of skin cancer (*1*). The defect is caused by mutations in the *DKC1* gene that encodes the protein dyskerin. This protein resembles the yeast protein Cbf5p, believed to be involved in the production of ribosomal RNA (rRNA) (*2*). In a recent issue of *Nature*, Collins and colleagues (*3*) now demonstrate that DKC may not be caused by a deficiency in rRNA, but rather by a defect in the maintenance of telomeres (the repeat DNA sequences at the ends of chromosomes).

The enzyme telomerase is responsible for adding DNA sequences to the ends of chromosomes, replacing the terminal repeats lost during replication. Telomerase, a cellular reverse transcriptase, is a ribonucleoprotein (RNP) composed of both RNA and protein components (see the figure). It adds TTAGGG repeats to the ends of telomeres by copying a template within its own RNA (*4*). Telomerase activity is present in the cells of the early mammalian embryo, in germ line cells, in certain proliferating stem cells (such as those of the hematopoietic system), and in almost all cancer cells. Most normal cells have little or no telomerase activity and show progressive shortening of telomeres throughout their lifespan, resulting in a limited proliferative capacity and eventual growth arrest. Introduction of the catalytic component of telomerase into these cells results in telomere maintenance and the bypass of growth arrest (*5*). There is much interest in understanding the regulation of telomere length, the identification of telomere-binding proteins, and the elucidation of the functions of the different telomerase components.

Collins and co-workers previously showed that the 3′ end of the RNA component of telomerase (hTR) has structural and functional similarities to the H/ACA family (hairpin-hinge-hairpin-tail) of small nucleolar (sno) RNAs (*6*). Sequence elements in H/ACA snoRNAs that are also found in hTR are required for RNA maturation and stability. In their new study, the investigators demonstrate that dyskerin, itself a component of H/ACA snoRNAs, interacts with the telomerase hTR (see the figure). Why should human telomerase associate with a protein component of the snoRNP complex that is thought to guide uridine modifications of rRNA? It is possible that dyskerin promotes the interaction of telomerase with the nucleolus (the site of rRNA and ribosome production). This might facilitate telomerase RNA processing or RNP assembly through the same cellular machinery that evolved to make ribosomes. In support of this hypothesis, it has been found that mammalian telomerase RNA associates with the nucleolus (*6*).

The sequence homology between dyskerin and yeast Cbf5p (*7*), together with the phenotype associated with a lack of Cbf5p (*2*), led to the proposal that DKC is a disorder of ribosome production (*8*). In the new work, Collins and colleagues show that normal dyskerin is a component of human H/ACA snoRNPs. But, they discovered that mutant dyskerin is evidently still able to carry out snoRNP functions, as it has no discernible impact on rRNA processing. Instead the authors found that in cells from DKC



End game. The human telomerase RNP complex. The RNA component of telomerase (hTR) contains a template region that directly binds to the G-rich overhang of telomeres at the ends of chromosomes (*4*). In association with the catalytic reverse transcriptase protein subunit (hTERT), telomeric repeats are synthesized. Telomerase-associated proteins (TEP1, a vault protein that physically associates with both hTR and hTERT) and p23/hsp90 (molecular chaperones that physically and functionally associate with hTERT) are also components of the telomerase RNP (*9, 10*). The protein components of snoRNPs including dyskerin—which associate with the H/ACA portion of hTR—may be important for the biogenesis, processing, or turnover of the telomerase RNP (*3*). Telomere-binding proteins that might interact with the hTERT complex are not shown.

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patients there is a decreased accumulation of hTR, reduced telomerase activity, and abnormally short tracts of telomeric DNA. Although the investigators could not rule out the possibility that some defect in ribosome biogenesis or other cellular process contributes to the syndrome, a telomere maintenance disorder is sufficient to account for the various disease phenotypes.

How could a mutation in dyskerin cause a deficiency in telomerase? Dysfunctional dyskerin could inhibit the stability or processing of the telomerase hTR, or the assembly, stability, or activity of the telomerase RNP. The investigators observed a reduction in the steady-state levels of hTR in DKC lymphoblasts and fibroblasts, which is consistent with a defect in RNA or RNP stability. Lymphocytes normally express telomerase when stimulated to divide. Activated DKC lymphocytes expressed much lower levels of telomerase than did lymphocytes from healthy individuals. Thus, DKC cells appear to have a relative deficiency in telomerase rather than a total lack of the enzyme. Still to be resolved is whether DKC isoforms act recessively, dominantly, or codominantly with respect to the wild-type protein. If the DKC isoform is recessive, would overexpression of wild-type dyskerin rescue the telomerase RNA deficiency?

Fibroblasts and lymphocytes from DKC-affected individuals demonstrate an age-dependent increase in chromosomal rearrangements that is consistent with telomere shortening. This results in the formation of telomeric fusions (including dicentrics), Robertsonian translocations, and ring chromosomes (*1*). So DKC may also be regarded as a chromosomal instability syndrome. The symptoms of DKC appear with variable onset in those tissues that proliferate rapidly (such as gut epithelia or bone marrow) and have the greatest need for telomere maintenance. Patients with this disease have an age-dependent increase in risk for developing certain cancers, such as epithelial tumors of the skin and gastrointestinal tract (*1*). This is consistent with a telomeric maintenance disorder that leads to chromosomal instability, telomeric rearrangements, and cancer progression. It will be interesting to compare telomere length in various tissues of DKC-affected and unaffected individuals and to address the extent to which telomerase-dependent maintenance of telomeres is required during embryonic development or in response to proliferative demands on specific differentiated cell types. It is now becoming clear that telomere maintenance requirements are likely to be more complex than a simple on/off switch.

The many phenotypes of DKC suggest that telomerase-dependent telomere maintenance is required to provide enough proliferative capacity for multiple types of somatic cells during the human life-span. This leads to the hypothesis that telomere maintenance defects could be causal in certain other human age-related diseases. This is in contrast to the requirement for telomerase in the mouse: in this animal telomere maintenance defects only become apparent after several generations (*4*).

Although we are beginning to identify an increasing number of telomerase and telomere-associated proteins, we need to understand how the telomerase enzyme complex interacts with telomeres, and how telomere maintenance in some tissues and telomere shortening in others affect the intact organism.

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PERSPECTIVES: MATERIALS SCIENCE

Imaging Elusive Solute Atoms

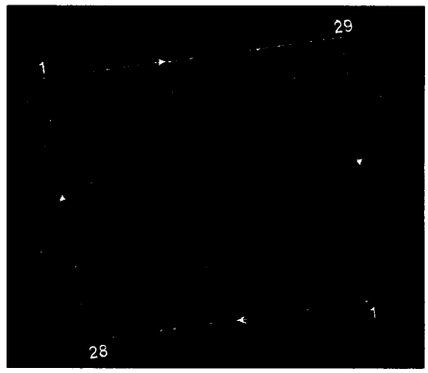
M. K. Miller

In 1948, Cottrell developed a theory in which the strength of iron was explained by the formation of "atmospheres" of carbon atoms around line defects (dislocations) in the crystal lattice (*1*). However, it took more than 50 years for his theory to be verified experimentally. On page 2317 of this issue, Blavette *et al.* (*2*) use a three-dimensional atom probe to determine the distribution of individual boron atoms around a dislocation in FeAl (see the figure), providing the first full experimental description of a Cottrell atmosphere.

According to Cottrell's theory, the smaller solute atoms present in steel, such as carbon, segregate to those regions of the crystal lattice around a dislocation that are compressed relative to the bulk, whereas larger solute atoms segregate to the dilated regions. These solute atmospheres pin the dislocation and make it more difficult for it to move, thereby increasing the resistance of the metal to deformation. The experimental verification of such solute atmospheres around dislocations long remained beyond the resolution of microscopes. In the last decade or so, solutes have been detected near dislocations by field ion microscopy, and solute concentrations have been characterized by atom probe field ion microscopy (*3*–*5*). However, the precise solute distribution around the dislocation core could not be resolved until three-dimensional atom probes were developed.

The three-dimensional atom probe (3DAP) combines the virtues of the field ion microscope (*6*) with those of the atom probe (*7*). Shortly after the concept and a prototype of the 3DAP were developed at Oak Ridge National Laboratory by the author in 1986 (*8*), substantially improved variants of the instrument were constructed at the University of Oxford by Cerezo *et al.* (*9*) and at the University of Rouen by Blavette *et al.* (*10*). These instruments, known as the position-sensitive atom probe (*9*) and the tomographic atom probe (*10*), respectively, are designed to determine the distribution of all the elements present in a material and have been used to study a wide spectrum of metals ranging from simple model systems to complex commercial alloys.

The 3DAP is the only instrument that can determine the identities of individual atoms in a material and measure their spatial coor-



Atom map of a Cottrell atmosphere. Each dot or sphere denotes the location of an individual atom. The figure has been oriented so that the aluminum (001) planes are visible as the nearly vertical lines of dots. The iron atoms have been omitted for clarity. The presence of a dislocation in this volume is indicated by the extra aluminum plane along the top of the marked box compared with the bottom. The boron atoms (red) are concentrated around the end of the extra plane, that is, the core of the dislocation. [From (*2*)]

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