soma-specific complex, DPY-27 alone is clearly not sufficient to direct binding of the complex to the X chromosome because both proteins are present but not associated with the X chromosome in XO males (*2*, 6). The chromosomal specificity is likely to derive from the elaborate regulatory hierarchy responsible for ensuring that the X chromosome dosage compensation machinery is activated only in the hermaphrodite (see figure) (*3*). Among the regulatory components is SDC-3, a zinc finger protein (*12*) that together with SDC-2 and DPY-30 is required for DPY-26 and DPY-27 localization (*1*, *2*). An as-yet-undefined interaction of SDC proteins with the DPY-27 complex or a change in X chromatin accessibility induced by the SDC proteins could result in the capture and stabilization of the dual-function proteins DPY-26 and DPY-28 on the X chromosomes during embryogenesis in XX hermaphrodites.

What are the implications for chromosome condensation? DPY-26 is a novel protein, but on the basis of immunolocalization data it is likely a structural component of the condensed chromosome. Studies in other species suggest that SMC family members are likely to play a role in general chromosome condensation in nematodes, so we may expect new members to be found as the germline partners of DPY-26. Interestingly, the structure of SMC proteins suggests a possible energy-dependent motor function that could be used for chromatin reorganization (*6*, *13*). Will distinct protein partners specify the extent of chromosome compaction achieved? Under this scenario, specialized partners for DPY-26 may have evolved to provide both X chromosome recognition and the ability to modulate condensation to achieve the fine level of gene repression critical for dosage compensation in the nematode.

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DEVELOPMENT

A Fin-de-Siècle Achievement: Charting New Waters in Vertebrate Biology

David Jonah Grunwald

In an accomplishment of historic proportions, reported as a group of 36 papers in the December issue of *Development*, scientists at the Max-Planck-Institut für Entwicklungsbiologie in Tübingen and Massachusetts General Hospital in Boston have initiated a systematic genetic analysis of how the vertebrate embryo is formed (*1*). Led by Christiane Nüsslein-Volhard and Wolfgang Driever, the groups have amassed and begun to analyze a collection of more than 1800 developmental mutants representing defects in about 500 different genes that contribute to the form and function of the zebrafish embryo. The seminal insights garnered from a similar analysis of *Drosophila* embryogenesis (*2*) were recognized last year by the Nobel committee, and we can expect that the current assault on the zebrafish embryo, which is unprecedented in its scale and method of approach in vertebrates, will have an equal impact on future research. The timing of the effort is superb, given the relatively recent appreciation of the degree to which both the molecules and the logic underpinning embryonic development are conserved throughout the vertebrates (*3*). As a result, the benefits to be accrued from analyses of these mutants are profound. We can anticipate that study of the zebrafish mutants will yield insights into the genes and mechanisms that coordinate normal vertebrate embryogenesis and that, when altered, result in a variety of inherited disorders in humans.

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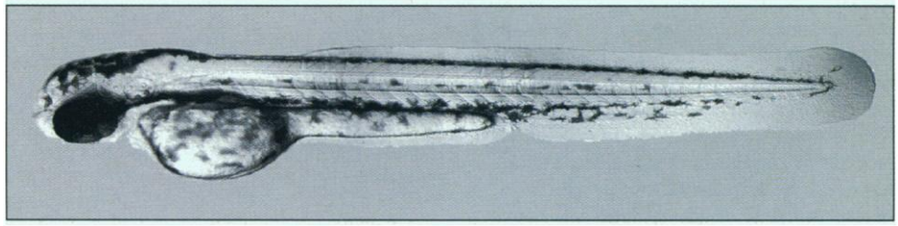

The subject. A 48-hour zebrafish embryo.

The zebrafish mutant collection identifies genes that participate in a wide variety of processes. Some mutations affect general cellular behaviors such as cell division and nuclear replication. Some mutations affect early processes critical for formation of the body pattern. A great many of the mutants were identified because they are defective in the formation of specific tissues or organs, including the notochord, somitic muscle, the ear, regions of the brain, the neural crest, the heart, and blood. In addition, two groups of mutations were recovered because they are likely to disrupt neural circuitry in specific ways. One class affects the control and coordination of locomotion behavior, and the other, recognized in Friedrich Bonhoeffer's laboratory in Tübingen, affects the neural connections formed between the retina and the optic tectum. Although the researchers point out that they have not identified all of the genes that might be mutated to a form that disrupts any of these processes, it is likely that a significant sample of such genes is represented in the mutants.

The zebrafish was chosen as a focus for the studies for several persuasive reasons. First, the external development and transparency of the zebrafish embryo mean that aberrant patterns of development can be recognized as they arise, giving the investigator a clue as to the time and place that the wild-type gene might normally function. Previous work, largely developed by the cadre of zebrafish laboratories in Oregon, had set the stage for an appreciation of mutant embryonic phenotypes by providing a detailed description of normal embryonic development in the zebrafish (*4*) and by analyzing in detail a few, particularly informative embryonic mutants (*5*), which alerted the zebrafish research community to the potential significance of

several developmental syndromes. In addition, recent studies in the field of experimental embryology have fueled advances in our understanding of how cell interactions and signaling pathways contribute to tissue formation (*3*), thereby providing a framework for the interpretation of the developmental syndromes. Hence, even at this early stage of characterization, the combination of early detection and existing conceptual frameworks allowed many of the gene functions identified in the zebrafish mutants to be assigned tentatively to specific candidate cell types or intercellular signaling pathways. A second reason the zebrafish was chosen as the focus is the extreme ease with which cells can be transplanted between mutant and wild-type zebrafish embryos, which allows for the rapid identification of the particular cells that normally provide the gene function missing in a mutant. Mosaic analysis also allows determination of which cellular defects are immediately caused by the mutation and which defects arise secondarily. This is especially important for understanding developmental syndromes where small early defects may initiate a cascade of associated, later-arising errors. Finally, the ongoing rapid development of tools for genomic analyses in the zebrafish (*6*) means that we can anticipate molecular identification and characterization of the genes that have been altered in the mutants.

The zebrafish screen was very much the conceptual heir of the famous *Drosophila* screen (*2*), incorporating a combination of attributes that distinguished it from other genetic analyses of vertebrate embryogenesis. Mutations were induced randomly throughout the genome with chemical agents that produce a broad spectrum of mutant alleles (*1*, *7*), some of which will reveal mild or tissue-specific functions of a gene. In the zebrafish and *Drosophila* screens, genes of interest were recognized solely on the basis of phenotypes exhibited by mutant embryos. The phenotype-driven approach immediately reveals the unique developmental role of a gene. Furthermore, it allows for the discovery of unanticipated gene functions. In addition, both screens were performed on a sufficiently large scale (about 6600 different zebrafish mutants were examined) as to identify groups of genes that together were required to carry out a single process, such as formation of a tissue. The isolation of sets of genes with similar mutant phenotypes is an exciting starting point for the identification of developmental and molecular pathways. In sum, the zebrafish mutant collection has unique virtues as a tool for the study of vertebrate development and will provide a much-needed complement to the mouse developmental mutants that are generated by targeting selected genes for mutagenesis.

Many of the early acting syndromes described in the initial reports fulfill the general expectations of prevailing paradigms in the development community (*3*). For example, recent studies in *Xenopus* have indicated that an antagonistic network of signaling factors conspire to generate a field of positional information across the dorsoventral axis of the pregastrula embryo, providing instructions for the allocation of early embryo cells to tissue-specific precursor pools. Several mutants in the zebrafish collection shift the field or its interpretation dorsally or ventrally. Similarly, signaling mediated by the product of the *sonic hedgehog* or a closely related gene has been shown recently to be involved in directing the development of the somitic musculature (*3*, *8*), and it appears that several of the mutants are likely to have defects in this signaling pathway. In contrast, other classes of mutants provide access to important biological processes for which there has been a dearth of animal models and for which we have limited understanding. Analyses of these mutants will help to identify cells and molecules that contribute to organ morphogenesis, direct the migrating neural crest cells to form their wide array of derivatives in appropriate locales, serve to guide axons to their appropriate targets, or are responsible for coordinating the activity of independent neural circuits. Fulfillment of only a subset of these heady expectations will dramatically increase our understanding of our own development and behavior.

Perhaps more subtle is the impact that the analyses of the zebrafish mutants will have on medical research. We might imagine that many viable developmental syndromes in humans are due to mild gene alterations, some of which are likely to be represented in the zebrafish collection. Several of the cardiovascular and hematopoietic mutants clearly phenocopy known human disorders (*1*, *9*). In addition, just as mutations in the *sonic hedgehog* gene proved to be responsible for one type of inherited holoprosencephaly (*10*), so we can expect that molecular identification of the zebrafish genes required for normal brain differentiation will provide a new category of candidate genes for nervous system disorders. Finally, one of the most prevalent yet confounding features of many congenital syndromes is the expression of constellations of errors in morphogenesis (*11*), such as associations between limb deformities and malformations of other tissues (for example, Holt-Oram syndrome). Similar examples of pleiotropy are evident in many of the zebrafish mutants. Analyses of the development of chimeric zebrafish embryos, composed of wild-type cells in some tissues and mutant cells in others, should help identify which arrays of defects arise as a result of the loss of a gene function that is needed at multiple independent stages of development (a pleiotropic syndrome) and which arrays arise as secondary consequences of a single primary defect (a sequence syndrome).

The large-scale screens for zebrafish mutants have opened our eyes to the potential of the zebrafish for uncovering genes that contribute to almost any facet of development or physiology. We may be at the end of a millennium, but developmental genetic studies with the zebrafish are far from fin-ished.

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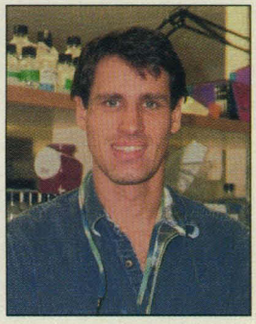
1996 Grand Prize Winner

Pharmacia Biotech and *Science* are pleased to announce the 1996 grand prize winner of the Pharmacia Biotech & *Science* Prize for Young Scientists. The winner of the 1996 grand prize in molecular biology was chosen from among the regional winners from four geographical areas: North America, Europe, Japan, and all other countries. The grand prize has been awarded to a regional winner from North America, Scott Seiwert, for his essay on RNA editing in trypanosomes. This essay, reprinted below, describes his doctoral research at Yale University.



Scott Seiwert

Dr. Seiwert was born and spent the early part of his life in Cincinnati, Ohio. As a teenager he lived in southern California. His interest in RNA arose as an undergraduate at the University of California, Santa Cruz, where he performed research on yeast pre-mRNA splicing in the laboratory of Manuel Ares. He received his graduate training in the Department of Molecular Biophysics and Biochemistry at Yale University in the laboratory of Joan A. Steitz and concluded his studies in absentia at Seattle Biomedical Research Institute in the laboratory of Kenneth Stuart. Early in the coming year, Dr. Seiwert will join the laboratory of Olke Uhlenbeck at the University of Colorado, Boulder, as a postdoctoral fellow.

Regional Winners

Europe. **Yen Choo** for his essay "Grasping the Double Helix: The Design of Sequence Specific DNA Binding Proteins," which is based on work performed at the University of Cambridge, Cambridge, UK.

North America. **Hwai-Jung Cheng**, for his essay "The EPH Ligand Family and Neuronal Topographic Mapping," describing work performed at Harvard University, Cambridge, MA, USA, and **Maria A. Schumacher** for the essay "Crystallographic Studies on the Purine Repressor: A Paradigm, Allostery, and a Novel Binding Motif," which reports work done at the Oregon Health Sciences Center, Portland, OR, USA.

Japan. **Tohru Mizushima**, for the essay "Molecular Mechanisms of Cellular Stress Recognition—Relaxation of DNA in *Escherichia coli* Cells and Induction of Heat Shock Protein," reporting work done at Kyushu University, Fukuoka, Japan.

All other countries. **Hilary Anne Vaughan** for "From Pig to Human: The Definition of the Major Pig Xenoantigen and the Development of Strategies to Prevent Hyperacute Rejection in Pig-to-Human Xenografts" on work performed at the University of Melbourne, Australia.

The other finalists were as follows: from North America, **Yong Liu**, **Hiten Madhani**, **Kornelia Polyak**, and **Hongtao Yu**; from Europe, **Oliver Sorgenfrei**; from Japan, **Masashi Kato**; and from all other countries, **Peter Revill**.

The full text of the essays written by the regional winners can be seen in *Science* Online in the Special Features/Beyond the Printed Page section: http://www.aaas.org/science or http://www.aaas.org/science/prize.htm.

RNA Editing Hints of a Remarkable Diversity in Gene Expression Pathways

Scott D. Seiwert

In *The Rescue: A Romance in the Shallows*, Joseph Conrad stoically proclaims "there is no rest for the messenger till the message is delivered." Although he could not have known, Conrad's statement serves as an apt metaphor for the dramatic remodeling of precursor mRNAs (pre-mRNAs) by the now familiar RNA processing reactions of higher eukaryotes. Although less explored, reactions required for gene expression in early diverging eukaryotes have demonstrated the generality of this metaphor within the eukaryotic kingdom.

Trypanosomatid protozoa represent a lineage of organisms that diverged close to the origin of eukaryotes, soon after the bacterial ancestors of mitochondria were engulfed (*1*). These organisms have received considerable attention because they pose significant threats to world health (*2*). Consequently, they provide an excellent means to examine the possible characteristics of gene expression in ancient eukaryotes. Studies of nuclear genes in trypanosomes have uncovered RNA trans-splicing, a process that may be a molecular fossil representing an intermediate step in the evolution from autoexcising introns to ribonucleoprotein particle–catalyzed intron removal (*3*). Examination of the expression of mitochondrial genes has identified a novel RNA processing reaction, termed RNA editing, that involves the transfer of genetic information between RNAs.

Mitochondrial DNA in trypanosomes is unusual in that it comprises two classes of circular molecules. The primary transcripts derived from the larger class of DNAs, maxicircles, have their coding information remodeled by the site-specific insertion and deletion of uridylate (U) residues (*4*). This sequence remodeling creates mRNAs homologous to those encoded by the mitochondrial DNA in other organisms and often produces more than 50% of a transcript's coding information.

RNA editing was initially thought to represent a challenge to the dogma that genetic information is encoded in nucleic acids because it adds sequence information after transcription. However, it was soon suggested that the sequence information required for this process is supplied by small RNAs transcribed from the second component of the mitochondrial DNA (*5*). These small RNAs, termed guide RNAs (gRNAs), have a sequence of approximately 10 nucleotides at their 5′ end that allows them to hybridize to a specific pre-mRNA at a defined location. Bulged purine nucleotides in the adjacent sequence of the gRNA are capable of directing the appropriate insertion of U's into the pre-mRNA, and U's bulged in the pre-mRNA could be deleted. Both of these events would extend the complementarity of the initial intermolecular duplex to produce a pre-mRNA containing the mature sequence. Thus, RNA editing could involve the transfer of genetic information from one RNA to another.

This model for RNA editing solved the dilemma for the central dogma, but raised the question of how sequence information is transferred between two RNAs. Several proposals were made for the mechanism of this reaction (that is, U insertion or deletion at a single site) (*5*–*8*). One popular model suggested that RNA editing is mechanistically

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