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Genomes: Epigenomics and the Future of Genome Sciences

Emerging data from diverse organisms indicate that we are only at the threshold of our understanding of the genome-wide implications of epigenetics. This relatively new field, entitled epigenomics, will be advanced by the recently completed sequence of the *Tetrahymena thermophila* macronuclear genome.

Laura A. Katz

Epigenomics encompasses genome-wide analyses of the growing list of epigenetic phenomena — such as DNA methylation, chromosome inactivation, non-Mendelian inheritance and programmed genome rearrangements [1–5] — that are found across the tree of life. One of these phenomena, programmed genome rearrangements, is central to the recently completed genome sequence from the somatic macronucleus of the ciliate *Tetrahymena thermophila* [6]. The epigenetic processes that generate ciliate macronuclei have parallels at both small and large scales across the eukaryotic tree of life (reviewed in [7]).

In contrast to many of the other 'omics' — proteomics, transcriptomics, metabolomics and so forth — epigenomics does not simply enhance genome sciences, but instead challenges the concept of the linearity between genome and phenotype (Figure 1). Definitions of epigenetics vary in the literature and range from Waddington's original description of the complex development of embryos (in contrast to preformationism) [8], to current usage such as "the transmission of information not coded in DNA sequences from cell to daughter cell or from generation to generation" [9]. In all cases, epigenetics enables a single genome to give rise to multiple phenotypes because of processes that are not simply encoded within the DNA sequence of the genome. Our growing appreciation of the role of epigenomics is evidenced by the dramatic increase in use of the term in recent literature (Figure 2).

Ciliate genomes are shaped by epigenetic processes. Like animals, ciliates have two distinct genomes: the germline micronucleus and the somatic macronucleus. In ciliates, however, both of these types of nuclei are contained within a single cell, rather than being sequestered into specific tissue types. The generation of the macronuclear genome in ciliates is driven, at least in part, by a genome-scanning process in which an RNA interference-based mechanism 'scans' the zygotic nucleus and the parental macronucleus to shape the newly developing macronucleus [10]. In *T. thermophila*, this processing is relatively limited, yielding ~225 chromosomes in the somatic macronucleus from five canonical eukaryotic chromosomes in the micronucleus [6,11]. In other ciliate lineages, this epigenetic processing is more extensive and can generate a macronucleus with ~25,000,000 gene-sized 'chromosomes' [12,13].

Analysis of the complete *T. thermophila* macronuclear genome sequence provides further evidence of genome scanning, as there is no evidence of any transposable elements in the macronucleus, even though transposable elements are found in available fragments of micronuclear DNA [6]. This suggests that genome scanning has removed foreign DNA that is present in the *T. thermophila* germline micronucleus. Full appreciation of the role of genome scanning in ciliates will

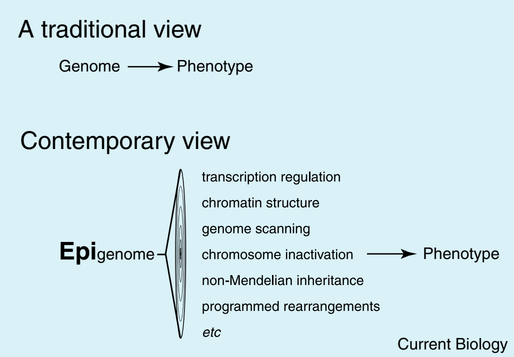


Figure 1. Epigenomics adds complexity to the relationship between genotype and phenotype.

require the complete sequence of the micronuclear genome from this strain of *T. thermophila* to allow detailed analyses of the type of sequences that are eliminated in creating the macronuclear genome, and the mechanisms underlying this epigenetic phenomenon.

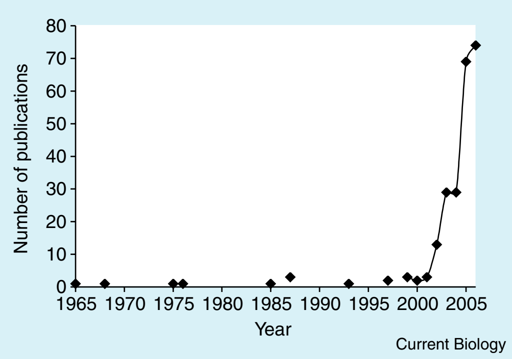
Several additional features make the *T. thermophila* genome particularly valuable to a broad community of scientists. The large number of genes in *T. thermophila* — estimated at 27,424 [6] — coupled with the genetic tractability of this organism enables functional studies of a diversity of genes; for example, homologs of disease-related genes from humans may be studied by knockouts in *T. thermophila*. Another related feature of the *T. thermophila* genome is the large expansion of gene families, including an estimated 1,525 genes for potassium channel proteins, which will serve as a resource for studies of the fate of gene duplications.

Analysis of the *T. thermophila* genome also sheds light onto the validity of placing this species in the eukaryotic supergroup 'Chromalveolata'. The controversial chromalveolate hypothesis posits that the common ancestor of the alveolates — which include ciliates, apicomplexa and dinoflagellates — and the chromists — which include diatoms, watermolds and brown algae — contained a chloroplast derived from a red algal endosymbiont [14–16]. Although this hypothesis predicts that the genome of *T. thermophila* should contain at least some genes derived from the red algal symbiont, rigorous searching failed to find such genes [6]. Hence, there is no compelling evidence of a footprint of photosynthetic ancestry in the *T. thermophila* macronuclear genome and therefore no support here for the supergroup 'Chromalveolata'.

To date, our understanding of eukaryotic genomes and their evolution is biased by the emphasis on analyses of animal, plant and parasite genomes. Yet, eukaryotic microbes have been the source for discovery of numerous genome features that have later been found to be widespread — for example, self-splicing RNA and telomeres in *T. thermophila* [17,18], and RNA editing within the mitochondrial genomes of *Trypanosoma brucei* [19]. Studies spurred on by the completion of the *T. thermophila* genome are likely to yield additional insights into the molecular mechanisms underlying epigenetics, as well as other as yet unpredicted phenomena. Such studies will further refine the relationship between the epigenome and the phenotype.

Figure 2. Use of term epigenomics in the literature.

Based on a search for 'epigenom*' from the Web of Science and Medline performed using the ISI Web of Knowledge site. Value for 2006 estimated assuming linear increase by calendar day as of 9/17/06.



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