VIEWPOINT

Evolving Genomic Metaphors: A New Look at the Language of DNA

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Recent genome-sequencing efforts have confirmed that traditional "good-citizen" genes (those that encode functional RNA and protein molecules of obvious benefit to the organism) constitute only a small fraction of the genomic populace in humans and other multicellular creatures. The rest of the DNA sequence includes an astonishing collection of noncoding regions, regulatory modules, deadbeat pseudogenes, legions of repetitive elements, and hosts of oft-shifty, self-interested nomads, renegades, and immigrants. To help visualize functional operations in such intracellular genomic societies and to better encapsulate the evolutionary origins of complex genomes, new and evocative metaphors may be both entertaining and research-stimulating.

Metaphors in science are like foghorns and lighthouses: They usually reside in treacherous areas, yet they can also guide research mariners to novel ports. With the recent flood of DNA sequences from the human gene pool (*1*, *2*) and those of other eukaryotic species, the exploratory ship of biology is suddenly up to its gunnels in data portraying a genomic seascape that is far more turbulent and evolutionarily fluid than formerly envisioned.

Evocative metaphors can distill an ocean of information, whet the imagination, and suggest promising channels for navigating uncharted genetic waters. For example, the metaphor of nucleotide sequences as encrypted language, translatable to the plain text of polypeptides, may have facilitated research in the 1960s that cracked the "genetic code." In a more recent example, the notion of the genome as a "book of life" helped to focus and sell the human genome sequencing project. However, metaphors can also mislead. The metaphor of the genome as a well-crafted blueprint or a finely tuned machine may have blinded many biologists to genomic imperfections attributable to phylogenetic constraints and evolutionary-genetic tradeoffs. Clearly, metaphors vary in utility and can influence research paradigms (*3*).

In the last century, "beads-on-a-string" was a prevailing metaphor for how housekeeping genes (those that encode proteins) were densely packed along each eukaryotic chromosome. Draft sequences of the human genome have nailed the coffin shut on that caricature: The coding "beads" make up less than 2% of our DNA, and most are themselves subdivided into beadlets (exons) interspersed with noncoding introns that comprise more than 95% of a typical transcription unit. Accordingly, some scientists next visualized protein-coding genes as tiny scattered oases in a genomic desert, implying that all else was a wasteland. Fortunately, this view did not prevent the genomic outback from being reconnoitered in the human genome project, because the results were truly incredible.

The intergenic wilderness proved to be populated by a motley crew of intriguing genetic characters: active promoters and regulators of gene expression, comatose pseudogenes, descendants of immigrant DNAs (perhaps horizontally transferred from microbes), vagabond sequences, hordes of tandem short-repeats, and great armies of repetitive elements—some with hundreds of thousands of like-uniformed members (*4*). Astonishingly, at least 50% of the human sequence is derived from transposable elements (TEs) that have dispersed themselves across the genome either as mobile DNA or via reverse-transcribed RNAs. Some of these smaller jumping genes are freeloaders that hitch rides on the backs of larger roving elements, like mites on fleas.

Nonetheless, the earlier metaphor of the intergenic region as barren desert probably still acts to divert attention from what could be highly fertile research terrain. Ironically, this genetic hinterland of regulatory tacticians, renegades, deadbeats, ramblers, and foreigners may be the real mother lode for deep intellectual treasures regarding life's functional and evolutionary modes. By prospecting and mining rich research veins for the interactions between protein-specifying genes and the great assortment of repetitive elements, regulatory sequences, and other noncoding DNAs, geneticists only lately have begun to excavate precious conceptual ores and jewels from these genomic quarries.

A long-standing genomic metaphor has described all genetic material as selfish, each DNA segment (functional or not) concerned first and foremost with its own transmission (*5*). One effective strategy for a DNA element is to contribute to the health of its host, because such behavior raises the element's hereditary prospects. However, the strategies of other "selfish genes" may harm the individual. Hence arose the metaphor of "parasitic DNA," which posits that many genetic elements reside and replicate within the genome at organismal expense.

By proliferating across the genome, mobile elements promote their own survival, but their sheer numbers probably add a metabolic burden to the cell. Furthermore, these genetic nomads are a major source of mutations, most of which are deleterious to the host. Is the parliament of good-citizen genes powerless during the evolutionary process to constrain these genomic outlaws? No, because natural selection at the level of organismal fitness in effect polices the net product of all DNA-level interactions, and is the final arbiter in all matters of genetic jurisprudence.

The genomic encyclopedias of life are revealing many surprising ways that transposable elements and housekeeping genes have coevolved within their cramped cellular quarters. Most important is the realization that some TEs (or their immobile offspring) also confer significant benefits to host genomes. For example, many TEs carry regulatory sequences that over evolutionary time have been drafted into the adaptive service of modulating gene expression. Many salubrious tasks for TEs have likewise been "host recruited," such as sponsoring variation at histocompatibility loci by serving as recombination templates, forming centromeric regions, replenishing telomeres, and promoting mutations and gene duplications that provide a fodder for evolutionary innovation (*6*).

Geneticists are gradually abandoning the view of intergenic regions as mere junk. If this metaphor is retained at all, it should be modified to picture these genomic tracts in the way that many anthropologists now view ancient garbage dumps—not as containing rubbish, but as holding important clues to people's daily lives in civilizations past. Likewise, DNA sequences outside the exons may be uniquely revealing about the coevolutionary lives of DNA within cell lineages. In short, metaphors can and should evolve to accommodate new findings.

One adaptable metaphor would liken each genome to a social collective whose DNA sequences display intricate divisions of labor and functional collaborations, yet that maintain partial autonomies of fate (due to sexual reproduction), resulting in occasional conflicts of interest. In this view, many types of DNA behavior roughly mirror those of hu-

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mans bound in tight social arrangements, such as communes. These include collaborative efforts, but also cheating; aggregate actions, but also personal opportunism; group alliances, but also conflicts; and parliamentary needs often opposed by egoistic tendencies. However, this metaphor neglects the clonal proliferation of elements possible within a genome, and the extensive reassortment of unlinked sequences that accompanies each generation of sexual reproduction. An Israeli kibbutz might be a closer analog of genomic society in this latter regard, because most marriages are outside the collective. It would be even better if a partially randomized clique of kibbutznikim in each generation married a comparable suite from another conclave to initiate each new commune!

Another metaphor might present each genome as a miniature cellular ecosystem with each gene occupying a particular functional niche, yet in which the DNA sequences have evolved elaborate interactions (including parasitism, commensalism, and mutualism) normally associated with species in natural biological communities. However, this metaphor falls short by failing to ascribe to genes the exceptional collaborative responsibilities also entailed in producing a discrete entity (the organism) whose survival and reproduction is key to the evolutionary game.

The hope for any metaphor in science is that it may bring otherwise unfamiliar subjects to life, make connections not otherwise apparent, and stimulate fruitful inquiry. A danger is that a metaphor can restrict rather than expand research horizons. Many genomic metaphors have elements of truth, and each may have its time and place. I doubt, for example, that a depiction of the genome as a molecular ecosystem would have served well in promoting or guiding the human genome project. However, perhaps the time is right for new panoramic images of the genomic landscape that capture proper notions of complexity and evolutionary dynamism. Although no one metaphor is likely to be informative in all respects, some new perspective that views the genome as an interactive community of evolving loci may be especially useful and stimulating at this time.

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VIEWPOINT

Harnessing Genomics and Biotechnology to Improve Global Health Equity

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With decisive and timely action, genome-related biotechnology can be harnessed to improve global health equity. In June 2002 in Kananaskis, Canada, leaders of the G8 industrial nations will develop an action plan to support implementation of the New African Initiative. By extending their discussion of health issues raised in the New African Initiative to include genomics, G8 leaders could signal their intention to increase global health equity by preventing a health genomics divide from developing. There are already some early and growing examples of genome-related biotechnology being applied successfully to health problems in developing countries. But how can genomics be systematically harnessed to benefit health in developing countries? We propose a five-point strategy, including research, capacity strengthening, consensus building, public engagement, and an investment fund.

It is 2010. The World Bank has just released a depressing report on *The Health Genomics Divide*. The report laments that the promise of genome-related biotechnology in the area of health, heralded a decade earlier by the sequencing of the human genome, has been denied those in the developing world. The unfolding revolution resulted in designer pharmacogenomics in rich countries and lost opportunities for advancing the health of those in Africa, Asia, and Latin America (*1*).

However, this future is not inevitable. Imagine what could happen if political leaders seized the opportunity to put this matter on the agenda of the world community. In June 2002 in Kananaskis, Canada, leaders of the G8 industrial nations will develop an action plan to support implementation of the New African Initiative (*2*). By extending their discussion of health issues raised in the New African Initiative to genomics, G8 leaders could signal their intention to prevent a health genomics divide from developing in the first place. This opportunity was lost in information technology (*3*) and agricultural biotechnology (*4*); it must not be lost in the area of human health.

Life expectancy in many developed countries is 80 years and rising; in some sub-Saharan African countries, mainly as a result of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), it is 40 years and falling. These and many other inequities in global health are major ethical challenges in the world today. With decisive and timely action, genome-related biotechnology can be harnessed to improve global health equity.

There are already some early and growing examples of this biotechnology being applied successfully to health problems in developing countries.

1) Diagnosis of leishmaniasis and dengue fever in some Latin American countries has already been improved by the use of polymerase chain reaction techniques. The pioneering work of Eva Harris of the Sustainable Sciences Institute (San Francisco, California) has documented that when appropriately implemented in Nicaragua, Ecuador, and Guatemala, techniques such as PCR and nonradioactive DNA probes are more rapid, sensitive, specific, versatile, safer, and less costly than prevailing methods for detection of pathogenic organisms (*5*, *6*).

2) Despite its embargo against Cuba, the United States has made a specific exemption and is willing to import the only meningitis B vaccine developed by the Carlos J. Finlay Institute in Cuba (*7*), attesting to the potential of biotechnology in developing countries. This vaccine is being tested in the United Kingdom and has been exported and licensed to at least a dozen other countries (*8*). Biotechnology now ranks third, behind only sugar and tourism, among Cuban industries. Cuba holds over 400 biotechnology patents. Brazil, which has its own rapidly evolving genomics and biotechnology industry, has imported several million doses of the Cuban meningitis vaccine.

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