Metaphors and the Role of Genes in Development

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Summary

In describing the flawless regularity of developmental processes and the correlation between changes at certain genetic loci and changes in morphology, biologists frequently employ two metaphors: that genes 'control' development, and that genomes embody 'programs' for development. Although these metaphors have an admirable sharpness and punch, they lead, when taken literally, to highly distorted pictures of developmental processes. A more balanced, and useful, view of the role of genes in development is that they act as suppliers of the material needs of development and, in some instances, as context-dependent catalysts of cellular changes, rather than as 'controllers' of developmental progress and direction. The consequences of adopting this alternative view of development are discussed.

Introduction

When dealing with complex problems it is useful and often necessary to use descriptive metaphors to voice our best guesses about causality and mechanism. Often such metaphors become the jargon of the field and efficient communication comes to depend on them. In genetics and developmental biology, powerful and evocative metaphors about genetic controls and genetic programs describe our intuition about the relations between genes and the processes that lead to biological form. The evocative power of these metaphors, however, tends to make us forget that they are no more than working hypotheses. In particular, now that their use has become widespread among biologists, it has become ever easier to believe that the jargon represents understanding and that the metaphors describe the mechanism rather than the model. The following quotations, taken from reviews and textbooks, illustrate the point and set the scene for the subject of this article.

'This collection of chromosomes in the fertilized egg constitutes the complete set of instructions for development, determining the timing and details of the formation of the heart, the central nervous system, the immune system, and every other organ and tissue required for life'[1].

'It has become increasingly clear that the developmental program resides in the genome, and that in most cases the environment provides only general stimuli and relatively little specific information'[2].

'We know that the instructions for how the egg develops are written in the linear sequence of bases along the DNA of the germ cells'[3].

'...a portion of the metazoan genome is specifically involved in the control of ontogeny and evolves by a mode distinct from those of structural genes'[4].

'We all recognize that in the fertilized egg there is a set of genes ... and that these genes give instructions that ultimately produce a complex adult.'[5].

While the sentiments expressed in these quotations may seem extreme to some, it is clear that many biologists subscribe to them, literally. The concepts that genes control development and morphology, that genomes contain developmental information, and that development follows a genetic program pervade modern thinking in molecular, developmental, and evolutionary biology. The genome is assumed to encode higher levels of organization. Genes and their products are seen as the causative agents of differentiation, and controlled gene expression is seen as the driving force of progressive change in development. The crucial regulatory role attributed to genes is emphasized by the widespread acceptance of the notion that a substantial number of genes are specifically concerned with the orderly progression of events during development[4]. As a consequence, it is assumed that an understanding of the mechanisms of gene regulation and of the detailed structure of the genome are not only fundamental to an understanding of development but virtually sufficient for this understanding. In the sections that follow, I will first explore the various metaphorical attributes that have been bestowed on genes and genomes, and show that these are ultimately unhelpful in developing a correct understanding of what genes really do and of how development proceeds. Although the issues explored here might seem to be mainly about terminology, they involve more than semantics; the metaphors of 'control' and 'programs' have shaped priorities in research and, to some extent, narrowed the range of investigation in developmental biology. In the concluding section of this article I will propose a fundamentally simple view of the role of genes in development that can be used as a working hypothesis at all levels of investigation on the function of genes.

The Metaphors

The belief that genes control and that genomes contain programs emerges from several observations about developmental genetics. First, mutation in certain genes, particularly the homeotic and segmentation genes, for instance those in the bithorax and Antennapedia complexes in *Drosophila*, can lead to very specific and often dramatic alterations in the body plan, in which nearly normal body parts develop in inappropriate locations or in which the characteristics of one body region are replaced with those of a different region[6–9]. Second, many of these genes have a homeo-

box or zinc-finger motif in their coding sequence, and are thus presumed to be regulators of transcription. It is therefore believed that their primary function is to regulate the expression of alternative sets of subordinate genes which, in turn, control the development of alternative complex morphologies[10,11]. Third, in many cases morphological evolution appears to be uncoupled from genomic evolution. Rates of DNA base-pair substitution and of protein evolution appear to be more constant among species than are the rates and degrees of their morphological divergence. This apparent discrepancy has led to the idea that there are certain genes responsible for morphology, and that these evolve under different constraints than those governing other genes[4]. 'Developmental' genes are thus assumed to be distinct from genes that perform 'housekeeping' duties.

We can summarize the current concepts about the relationship between genes and development as follows: genes control development; the genome contains a program for development; a specific set of genes has evolved that is exclusively concerned with development. Below we will examine the logical basis of these assertions.

Do genes control development?

To 'control' a process means to exercise a directing or restraining influence over it. Certain gene products undeniably play a role in determining which of several possible developmental events takes place. Changes in the expression of such a gene can have a cascade of consequences that become manifest as a change in a developmental pathway. Such genes can thus be said to control alternative developmental pathways, just as the steering wheel of a car controls the direction of travel. However, this is far from equating the steering wheel with the driver.

When we trace the causal pathway of a developmental event[12], we may often (but not necessarily always) encounter a gene whose product is required for that event, and without which that event would not take place. But the causal pathway does not end there. The expression of the gene or the activity of its product must itself be controlled by a specific stimulus, perhaps an ionic or organic inducing molecule, or through the product of a regulatory gene. Regulatory genes, in turn, owe their timely activity to stimuli external to themselves, and so forth. The causal pathway is endless and involves not only genetic, but manifold structural, chemical and physicochemical events, a defect in any of which can derail the normal process.

When a gene product is needed, a signal from its environment, not an emergent property of the gene itself, activates expression of that gene. When a non-genetic substance is needed, gene products may cooperate with other components of the cell to synthesize or import it. Thus genes do not provide instructions for development, but they aid in supplying the material basis for development. Furthermore, the causal pathway is seldom if ever linear, but contains loops and complex reticulations. Thus, when we speculate about the control of a developmental process, it is misleading to assign a controlling role to a particular gene.

The limits of usefulness of the idea of control when applied to particular genes can be seen from the results concerning a classic 'control' gene, *Antennapedia* of *Drosophila*. Schneuwly *et al.*[13] fused *Antp* cDNA to a heat shock promoter, then constructed flies carrying the construct and heat pulsed these animals during development. As might be expected, transformations of antennal into leg structures were produced. The special interest of the experiments may lie, however, in the fact that these transformations showed neither 100 % penetrance nor completeness of transformation within the affected individuals, even though one may presume that the expression of the gene took place in virtually all cells. Furthermore, while transformations were obtained if the heat pulse was given in embryos or late third instar larvae, none were obtained if the heat pulse was given during the first or second larval instars. In other experiments on *Antp*, Jorgensen and Garber[14] studied transcript patterns in the eye-antenna discs of *Antp* mutants and concluded that production of the transcript was often much broader within the discs than the extent of the phenotypic transformations would indicate. In all these results, it is apparent that expression of a 'controlling' gene is in itself insufficient to 'control' the phenotype. In a system in which *every* component, *and* past history, all have to come together at the right time and in the right proportions, it is difficult to assign control to any one variable, even though one may have a disproportionate effect.

Does the genome contain a program for development?

The very orderly progress of development and the flawless repetition of an identical and complex sequence of developmental steps in countless individuals suggests the existence of an underlying program. Furthermore, that there is, in some sense, a genetic foundation or set of tight constraints on development is obvious from the species-characteristics of development and the effects of mutations on developmental processes. Since genes and maternal oocyte cytoplasm are the only matter that is passed from parents to offspring, it is compelling to assume that genes or the genome as a whole must somehow contain or embody a program for normal development. But is this necessary and logical? A program implies the existence of a code and a sequence of instructions. Does the fact that in most cases gene expression in development is sequential constitute a program? Two conditions must be met for this to be true. First, the sequence from gene to process must be causal, that is, the gene or its product must be necessary and sufficient for the occurrence of the process, and not be itself provoked by the process. Without such a stipulation the relation becomes trivial; e.g. a bouncing ball consists of a sequence of causal reactions, but this does not mean that the ball is programmed to bounce,

nor is it useful in an analysis of the physics of bouncing to suppose that such a program might exist. Since many genes encode enzymes which catalyze biochemical reactions that would otherwise occur at imperceptible rates, their gene products could be said to cause a certain chemical reaction to occur. While in a thermodynamic sense this is not strictly true, since the enzyme is merely a catalyst, we can stretch the point and say that an enzyme 'causes' a reaction to occur in a biologically useful time frame. If we go to a slightly more complex case, however, the assertion of causality becomes meaningless. For instance, actin and tubulin genes are necessary for morphogenetic movement to occur. A deficiency in these genes (or in any gene or process that affects the synthesis or localization of actin and tubulin) would prevent or severely distort much of morphogenesis. These genes do not, however, 'cause' or 'control' morphogenesis; they enable it to take place. Similarly, axiation in animal embryos is dependent on the proper spatial distribution of maternal cytoplasmic determinants. While determinants may be the products of single genes, their proper effect depends as much on their spatial distribution as it does on their chemical nature. The precise localization and graded distribution of the *bicoid* gene product of *Drosophila*, for instance, requires the presence of several other specific gene products, as well as an interaction with structural elements in the oocyte cytoplasm. Proper axiation fails if *any* of these factors are deficient. Thus, control of axiation is diffusely distributed among gene products and structural elements and not emergent from the genome alone.

Second, a program must somehow contain information about the temporal sequence of events. This criterion is never met[15]. Development is a series of elaborate temporal and spatial interactions that are context dependent[16]. The sequence of gene activation we see in development is an emergent property of this interaction (again, the bouncing ball analogy). The genes whose products are necessary during development are activated by stimuli that arise from the cellular and chemical processes of development. Thus the network or pattern of gene activation does not constitute a program, it is both the consequence of, and contributor to, development.

The only reasons for supposing the existence of a program for development are first, that *we* would have designed such a system that way, and second, that it is discomforting to deal with the notion that development is largely self-organizing. The main difficulty in accepting development as a self-organizing process is that we do not have a simple description of heritability and self-replication for such a system. The complexity of the complete developmental process, from fertilized egg to fully formed embryo or fetus, precludes such a description at present but when we analyze any *particular* aspect, such as the formation of the dorso-ventral axis in amphibian embryos[17], it is clear that such self-organizing properties are involved and that specifying *all* the participating gene products would give an impoverished description of the process.

Is developmental information encoded in the genome in any way?

In biology the term information is used with two very different meanings. The first is in reference to the fact that the sequence of bases in DNA codes for the sequence of amino acids in proteins. In this restricted sense, DNA contains information, namely about the primary structure of proteins. The second use of the term information is an extrapolation: it signifies the belief or expectation that the genome somehow also codes for the higher or more complex properties of living things. It is clear that the second type of information, if it exists, must be very different from the simple one-to-one cryptography of the genetic code. This extrapolation is based, loosely, on information theory. But to apply information theory in a proper and useful way it is necessary to identify the manner in which information is to be measured (the units in which it is to be expressed in both sender and receiver, and the total amount of information in the system and in a message), and it is necessary to identify the sender, the receiver and the information channel (or means by which information is transmitted). As it is, there exists no generally accepted method for measuring the amount of information in a biological system, nor even agreement of what the units of information are (atoms, molecules, cells?) and how to encode information about their number, their diversity, and their arrangement in space and time[18–20].

The Functions of Genes

If the genome contains no program, and if genes contain no information about levels of organization higher than the primary structure of proteins, then what is the function of genes in development, and how do we explain the programmatic regularity of development? As it turns out, we already have a good working model for interacting networks that involve real gene products and that exhibit regulation as well as spatial and temporal diversification. This model system consists of the multitude of metabolic reactions that are catalyzed by enzymes. The interactions and shunts in the biochemical pathways of biosynthesis and catabolism are regulated and integrated at various levels. Some control of direction and timing is simply by mass action (usually through upstream regulation of substrate availability); other regulatory mechanisms involve the expression of inducible enzymes. In addition, there are innumerable examples of specific activation and inhibition of enzymes either by allosteric activators and inhibitors that themselves are temporally or spatially regulated, or by feedback or feed-forward inhibition. While some gene products are present constitutively, others are induced or repressed by precursors or products of specific reactions.

The intrinsic (or extra-genetic) regulation of metabolism is usually regarded as a 'housekeeping' function, involving the products of so-called housekeeping genes that are usually set apart conceptually from the genes that 'control' development[4]. Yet metabolic and biosynthetic pathways are regulated with a degree of precision and specificity that rivals any developmental process. Shunts have evolved that are regulative and that deal with a variety of environmental contingencies, and precise regulation of important cellular functions often occurs with constitutive enzymes (thus without regulation of gene expression). The manner in which gene products 'regulate' intermediary metabolism provides us with as nearly perfect an analog (or model system) as possible of the way in which genes 'regulate' development. Transcriptional regulatory genes can be comfortably included in such systems without being assigned the exclusive property of 'control'.

In this view, putative transcriptional control that affects alternative developmental pathways, such as those of the bithorax and Antennapedia complexes in *Drosophila* or the *lin* genes in *Caenorhabditis*, can be seen as part of the network of interactions rather than as directors of the scenario. The effects of other less well categorized genes whose mutants show large aberrations can also be seen in an appropriate context. For instance, in vertebrates, the genes that are involved in the cyclopic otocephaly in guinea pigs[21] could be construed as 'developmental' genes since defects in these genes cause an inhibition of organization by the prechordal mesoderm[22]. But analysis of penetrance and expressivity in this system has shown that environmental factors are of overwhelming importance in determining the exact expression of this bizarre phenotype. Regulatory genes are undoubtedly active in early embryonic development in vertebrates, as they must be throughout development and metabolism in all organisms, but their function is not to 'organize' development. Their products, or those of the genes they regulate, most probably affect the dynamics of one or more physiological or interactive processes. Such processes, in turn, lead to a cascade of inter- and intracellular reactions, both physical and chemical, some of which may require the action of additional gene products, and some of which have sufficient effects on the cellular and supracellular behavior to be interpreted as patterned differentiation and morphogenesis. Models that explore how this might occur are abundant[23–33].

None of the preceding concepts are new to biological thought. Textbooks of genetics and evolution in fact caution against the simplistic interpretation of genotype to phenotype mapping and point out the futility of asking questions about how many genes are required to make a character. Most speak of genes as 'affecting' characters, not 'controlling' them[34,35]. The only question that can be sensibly asked about the relation between genes and form is whether, when individuals differ in a character, that *difference* is due to differences in genetic or in environmental factors[36,37]. When a character is changed in consequence of mutation at a single genetic locus we can eventually use this information to pinpoint the time and place in development in which that gene's product was required for normal progress. This is true whether the gene codes for a structural protein or an enzyme, or whether it is a regulatory gene at whatever hierarchical level.

The simplest and also the only strictly correct view of the function of genes is that they supply cells, and ultimately organisms, with chemical materials. These materials can be the gene products themselves, but often they are things made, altered, or imported by the gene products. The most generally useful hypothesis about the function of genes is the following: Genes are passive sources of materials upon which a cell can draw, and are part of an evolved mechanism that allows organisms, their tissues and their cells to be independent of their environment by providing the means of synthesizing, importing, or structuring the substances (not just gene products, but all substances) required for metabolism, growth and differentiation. The function of regulatory genes is ultimately no different from that of structural genes, in that they simply provide efficient ways of ensuring that the required materials are supplied at the right time and place.

Postscript

What are the implications of this view for the study of molecular genetics, development and evolution? The realization that genes act as the suppliers of material suggests not so much a change in practice as a change in emphasis from a gene-centered view of living things to an interactive components view in which genes are necessary but far from sufficient. Several of the more obvious consequences are listed below. Some of these are already recognized as important parts of many research programs and conceptual frameworks; others suggest shifts in emphasis or new areas worthy of consideration.

1) The expectation that the structure of a genome will reveal higher organizing principles is unfounded, and the search for such principles is likely to be frustrating and counterproductive because it deflects attention from the intracellular and intercellular interactive processes that are the real regulators of development. To the extent that genome analysis programs are predicated on the belief that the results will 'explain' developmental outcomes, they are misguided.

2) Study of the structure, regulation, and evolution of biochemical and metabolic reaction networks both in their own right and as analogs of developmental control mechanisms should be encouraged.

3) If genes indeed evolve as components of mechanisms to achieve increasing independence from the environment, then one would predict that the evolution of genetic complexity should not be in strict lockstep with the evolution of structural complexity. In addition, one would predict that the degree of morphological

differentiation between related species should be positively but not strictly proportionally related to the degree of genetic difference between them. This is because form emerges from interactive processes and genes are not the direct cause of the development of specific forms. (Uncoupling of genotypic and phenotypic evolution can also be explained under a neutralist model that assumes much of the DNA to be irrelevant in the development of phenotype; it thus might be worthwhile to investigate the differences between predictions made on either model.)

4) New approaches need to be found to deal with the heredity of form. Quantitative genetics seems one of the most promising approaches for analyzing the heritability of complex characters, but the theory is still too poorly developed to deal with the many interactions (epistasis, collaboration, non-linearity) that are of crucial importance in development. The analysis of phenotypic and genetic variance-covariance matrices[38–40] may provide an interesting approach to identifying structures whose development is integrated in various ways. But ways need to be found to describe, measure, and analyze variance in developmental *processes* because these are the ultimate determinants of form.

5) The reason that pattern and form exhibit heritability is that they develop under a specific and restricted set of physical circumstances. When these circumstances are altered, whether by changes in gene products or by changes in their environment, a different pattern, equally heritable, develops. Changes in the heritable phenotype that are caused by changes in the environment are referred to as the *norm of reaction* and have occasionally been studied from an evolutionary perspective[34,35,41,42]. Since genes do not 'code' for form, but form emerges out of an interaction of gene products and environment, it is clear that the norm of reaction deserves more widespread study. This is, in part, also a call for a resumption of the research program initiated by Waddington[43,44] on 'canalization' of the phenotype.

6) If genes do not control development, then an effort is needed to devise methods aimed at detecting points in development where regulation does occur so that the processes responsible may be studied. For instance, at some level of microanatomy there is enormous variability in the pattern of almost everything in development; the precise pattern of cellular events at gastrulation or during osteogenesis is very variable, as is the cell-level anatomy of almost all structures from leaves to limbs. Yet at higher levels of organization the variability in these systems is greatly diminished. It seems reasonable to suppose, in the first instance, that regulation takes place at or just below the hierarchical level at which regularity is observed. Thus high variability at the cellular level in the presence of high constancy at the tissue level suggests the operation of regulatory mechanisms that act in cellular collectives. Such observations can help define the level at which we might search for control mechanisms.

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