Perspectives

Developmental mechanisms: putting genes in their place

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1. Introduction

Developmental biologists study changes in shape and form of embryonic tissues, the differentiation of their constituent cell types, the patterned arrangement of the resulting cells, and the intricate interplay among all these processes. Living tissues are first and foremost condensed materials, with inherent physical properties in common with their nonliving counterparts. But there are also significant differences: whereas nonliving materials often undergo alterations in their physical state without changing their chemical composition – water freezes and evaporates, lava flows, rubber stretches – embryos generally proceed from one state to another by adding or removing key ingredients. By switching genes on and off in space and time, new catalysts and structural components are placed at new sites and complex arrangements of cells and tissues ensue.

It is therefore often claimed that biological forms and characters are produced by "genetic programs". But while a close mapping between patterns of gene activity and morphological development is seen throughout the biological world, this correspondence does not necessarily imply that genes "program" organismal characters. For obvious reasons, such relationships have only been observed in modern, highly-evolved organisms. Ancient forms in which redundancies, parallel pathways and other buffering mechanisms had not yet evolved were likely to have been much more loosely organized, without the same program-like association between genes and form (Newman 1992, 1994; Newman and Müller 2000; see below).

As a developmental biologist whose original training was in the physical sciences, I have always had difficulty with a set of views that asserted that biological form was, on the one hand, programmed in every important detail by code written in a specific medium (the genes) whose original function (specifying the primary structure of proteins) had no obvious connection to three-dimensional cellular organization and, on the other hand, was the evolutionary product of small, incremental, structural alterations brought about by purely random changes in the hypothetical "program". Like the notion that Shakespeare's works could be produced in sufficient time by a hundred monkeys chained to typewriters, such a scenario is nearly impossible to falsify. And I suppose the fact that few convincing scientific alternatives have been put forward has given it staying power. But it also seems a reasonable expectation that the sciences that deal with the morphological transformations of materials would have something important to contribute to unifying our understanding of the generation of form in ontogeny and phylogeny. With this in mind, it made sense to approach the question of what factors, other than genes, may be determinants of morphological development, by working backward from modern gene-form relationships to conceptualize the kinds of organisms that are likely to have existed at the dawn of multicellularity (Newman 1992).

Since inherited change in a character of a modern organism typically requires changes in corresponding genes, the standard view holds that inheritance of biological specificity (i.e. traits that distinguish one form from another) is just a matter of inheritance of specific genes. Biological inheritance is referred to as "particulate" (Mayr 1982) since genes are finite in number, separate and independently assorting. This atomistic picture prevails despite recognition of variability in penetrance of genes' effects, multifactoriality and functional redundancy of gene action in the determination of

characters, and the existence of allelic interactions and epigenetic processes in inheritance (Jablonka and Lamb 1995; Hollick *et al* 1997).

But, of course, it is not characters (cell types, segments, bristles, digits, and so forth) that are inherited as "particles", just the genes that contribute to a character's construction, and whose alteration may potentially alter its properties. That characters themselves are *not* inherited in a particulate fashion was Mendel's own view. In discussing the class of features whose inheritance was tied to his "factors" or "elements" (he made no claim that all features were so tied) he stated: "the distinguishing traits of two plants can, after all, be caused only by differences in the compositions and grouping of the elements existing *in dynamical interaction* in their primordial cells" (Mendel 1866, p. 42; trans. Stern and Sherwood 1966; emphasis added). And while the "unit character" notion was considered problematic and dismissed early on by such pioneers as Johannsen and Morgan (Dunn 1965), it still lives on. Mayr, in his influential *Growth of Biological Thought*, for example, characterizes Mendel's major contribution to biology as "[h]is inference that *each character is represented* in the fertilized egg by two, but only two, factors, one derived from the father and the other from the mother, and that these could be different" (Mayr 1982, p. 721, emphasis added). The main role of the notion of particulate inheritance appears to be the warranty that all organisms are "Mendelian" entities (that is, their traits are genetically determined) even though most traits are not inherited in a "Mendelian" fashion.

But if characters are not, in fact, inherited as particles representing them in the germ cells, how are they transmitted from one generation to the next? Since there are no distinctive genes for fingers, wings, eyes, or appetite (although there are, of course, genes whose mutation can alter these features) the realization of these features during individual development must fully depend on the dynamical interaction (as Mendel put it) of the genes in the context of material systems in which they are found. This, in turn, implies that the laws governing the behaviour of such systems are at least as determinative of morphological and other phenotypic outcomes as is the programmed expression of genes.

The "generative" aspect of the transmission of traits has been recognized by previous workers (Ho and Saunders 1979; Oyama 1985, 2000; Nijhout 1990; Kauffman 1993; Goodwin 1994), and some discussions have explicitly incorporated an "environmental" dimension into the origination of phenotypic novelty (Johnston and Gottlieb 1990; see also Müller and Newman 2002 and references therein). Moreover, recent analyses have shown that the term "gene" has been employed in different ways when applied to developmental and evolutionary questions and that the gene concept has continued to evolve in concert with new discoveries in cellular biochemistry and comparative genomics (Griffiths and Neumann-Held 1999; Wu and Morris 2001). The reader is referred to the above papers for discussions of the meaning of the gene in these different contexts, which is not the purpose of this Perspective.

The remainder of this article is devoted instead to presenting and exploring the consequences of the view that the origination of metazoan forms lay in non-programmed, self-organizing material properties of cell aggregates, and that gene evolution has played a largely consolidating and integrating role in the ontogenetic realization of these forms. In particular, I suggest that the apparent agency of programs of gene expression in the development of modern organisms reflects the evolutionary recruitment of genes after the fact to stabilize and reinforce pathways for structures that originated by nongenetic processes, rather than the primacy of genetic mechanisms in the production of biological form. This, in turn, implies that a causal understanding of morphogenesis must adopt a "physico-evolutionary" approach rather than the "reverse-engineering" strategy that currently dominates developmental studies.

2. Genes, physics, and the evolution of development

Before the advent of multicellular organisms in the Precambrian, more than a billion years of prior evolution had produced eukaryotic cells with sophisticated protein synthetic machinery and repertoires of proteins sculpted through natural selection to perform a wide range of cellular functions. Multicellularity arose in ancient populations of cells that remained attached to one another after division, in populations in which cells became secondarily aggregated, or most likely, by each of these routes (Bonner 1998). The earliest multicellular forms thus consisted of adherent cells whose genes had evolved mainly to serve single-cell functions rather than global developmental coordination.

It is undoubtedly the case, however, that generation of body plans and organs in modern metazoan organisms is under the control of complex, hierarchically-organized, program-like routines of gene expression (Davidson 2001). The nature of the relationship between mechanisms of gene control and production of multicellular form must therefore be confronted first at the earliest stages of the evolution of development. How did complex body plans and organ forms first arise? More specifically, did elements of morphological organization emerge coordinately with incremental molecular genetic changes (the Neo-Darwinian default mechanism), or are structural

and genetic change evolutionarily decoupled from one another, with morphological change capable of leaping ahead of genetic change from time to time?

That morphological innovation can burst forth after only modest genetic change (or even alteration of the external environment) may be appreciated from recent experimental work on somitogenesis in vertebrate embryos. Segmentation is a well-studied body plan motif which is generally recognized to have arisen several times in the evolution of the metazoa. The vertebrate segmental plate becomes sequentially partitioned into paired somites by a process that involves an intracellular biochemical oscillator – the *c-hairy1* gene product (Palmeirim *et al* 1997). With the involvement of a gating event – a travelling wave of another molecule (Cooke and Zeeman 1976) or the cell cycle itself (Newman 1993) – this temporal periodicity becomes converted into a spatial periodicity (the somites) as cells with alternating adhesive properties emerge from a growth zone. Coordination between two physical processes – chemical oscillation and differential adhesion – leads to a situation in which the dividing cell population has the potential to add not just one new segment, but an indefinite number of them, to a preexisting unsegmented form. The coupled physical processes that perform this generative feat are inherent properties of cells: the spontaneous dynamics of biochemical networks containing positive and negative feedbacks and the stickiness of the cell surface.

These "generic" properties (Newman and Comper 1990) were latent in the primordial unsegmented cell mass (and indeed, in the free-living cells that preceded it) and needed only to enter into any of a broad set of quantitative relationships with one another to constitute a segment-generating machine (Newman 1993). Whether the appropriate ratios of physical parameters are attained by mutations in rate-determining enzymes or by external changes (temperature, nutrient levels) that retune dynamic metabolic processes, is immaterial. New forms brought about by environmental triggers will persist as long as the new environment does. Genetic change in individuals of the transformed population can lock in the novelty after the fact, making it resistant to potential reversal of the external trigger.

Segmentation is only one ancient morphological motif whose origination may be attributed to generic physical processes. The tissue segregation and multilayering of gastrulation, formation of intra-tissue cavities and lumina, and synchronic (in addition to progressive) formation of repeating structures, can all, in principle, be traced to inherent material properties of cell aggregates, such as differential adhesion and coupling of chemical reaction with diffusion (Steinberg 1998; Turing 1952; Newman and Comper 1990; Müller and Newman 2002). We have hypothesized that these material properties are also, in fact, the originating determinants of metazoan body plans, yielding structural templates for the accumulation of reinforcing genetic circuitry (Newman and Müller 2000).

An implication of this view is that ancient multicellular organisms with the same genotype exhibited multiple morphological phenotypes. In the absence of the stabilizing and integrating genetic circuitry accumulated between the period of morphological origination and the present, organisms would have been highly susceptible in the generation of their forms to temperature and other aspects of the physicochemical environment. These ancient organisms constituted a "pre-Mendelian" world (Newman and Müller 2000), in which genotype was only loosely correlated with morphological phenotype, and gene mutation did not lead to phenotypic alteration with nearly the regularity seen in modern forms.

3. The convergence of genotype and phenotype

Neo-Darwinian theorists minimize the importance of scenarios in which characters that first emerge by interaction of organisms with their environments later become incorporated in a genetic form into the developmental repertoire (Simpson 1953). [This is often referred to as the "Baldwin Effect", after J Mark Baldwin's 1896 paper "A new factor in evolution" (Baldwin 1896)]. First, it is a tenet of the neo-Darwinian framework that phenotypic plasticity can only have evolutionary consequences if its expression is tied to underlying genetic variability, but the Baldwin effect can, in fact, operate without such preexisting variability. The phenotypic plasticity that fuels it can just reflect the malleability of any physical system in a variable environment and selection can occur on genetic variation that may appear later, in a subpopulation that already expresses the trait (West-Eberhard 1986). Variants that confer stability in the face of internal noise or external inconsistency will increase over time simply based on the premium on breeding true of any ecologically-established organism (Salazar-Ciudad *et al* 2001a,b).

Second, the Baldwin effect makes neo-Darwinians uneasy because the vector from individual phenotypic change to genetic change appears to contravene the population-based viewpoint of the New Synthesis. Indeed, a scenario in which new gene variations are selected in relation to their ability to reinforce a novel, nongenetically-originated phenotype, is an inversion of the standard neo-Darwinian picture of incrementally building up a new phenotype by selection of preexisting genetic variants of minor phenotypic effect.

The neo-Darwinian synthesis, of course, does admit the possibility of selection that reinforces a given phenotype; such phenomena have been studied under the rubric

of "stabilizing" (Schmalhausen 1949) or "canalizing" (Waddington 1942) selection and have respectable, albeit marginal status in the standard picture. The reason for their lack of prominence is clear – it is difficult to see how such mechanisms (again, applied to modern species), can promote overt morphological, as opposed to covert molecular, evolution.

The only form of morphologically productive evolution in the standard model, then, is "dynamic" (Schmalhausen 1949) selection, which is inevitably incremental. The incrementalism of neo-Darwinism is based on two interconnected tenets of the theory. First, the basic assumption of this picture is that genotype determines phenotype, and, as noted above, any morphological variant that can contribute to the next generation will have a genetic basis. Second, there are compelling population biological arguments that "mutations of large effect" will not become established in natural populations (Fisher 1930). The "hopeful monsters" (Goldschmidt 1940) produced by such mutations in modern organisms would, with virtual certainty, be maladapted to their environment and reproductively exiled. Population-based natural selection (in this picture, at least) can therefore only produce morphological evolution by increments.

The barrenness of stabilizing evolution and the pathology of large-effect mutations, however, pertain to organisms whose generative potential is extensively canalized, and which are well-adapted to specific ecological niches, i.e. modern species. On the contrary, in the ancestral organisms hypothesized above, whose forms were highly dependent on physical processes, such considerations would not hold. For such polymorphic entities, stabilizing evolution paradoxically *depends* on mutations of large effect, but in this case the effect is to select out one of the several forms consistent with the organism's genome and cause it to be independent of external physical determinants. For example, if a self-organizing, physically-based segment-forming system generated zero, seven, or 25 segments, depending on the ambient temperature, a mutation of large effect in one of the organism's genes could ensure that only seven segments got made, regardless of the temperature. This might narrow the organism's niche occupancy, but the resulting forms would be neither unprecedented, maladapted, nor reproductively incongruous.

The significance of such an example (which is hypothetical, of course, but see below) is that in a world in which large-scale integration of spatiotemporal gene expression with morphogenesis has not yet occurred, stabilizing evolution, the Baldwin effect, etc. promote the "convergence" of genotype and morphological phenotype. These processes eventually result in "programmed" development, but the programs are not written in a genetic language.

4. Unprogrammed morphogenesis

The previous discussion contemplated the changing relationship between genes and form in a world of organisms initially quite different from the one with which we are familiar. It is implausible, though, that canalizing processes leading to genotype-phenotype "convergence" has advanced uniformly in all taxa and lineages. Our speculations imply that morphological plasticity is a primitive property of metazoans rather than primarily a sophisticated set of adaptations (Kirschner and Gerhart 1998). If this is correct it should be possible to find traces (or more) of externally-conditioned morphological plasticity disconnected from adaptive histories, and incipient mechanisms for its genetic integration, in at least some modern organisms.

A neo-Darwinian perspective would, in the first approximation, seek "evolutionary rationales" for any morphological motif, since the form would be presumed to have arisen through sequences of incremental variation, tested at each point for adaptive advantage. A more nuanced view would take into account the emergence of structural byproducts with no adaptive rationale (Gould and Lewontin 1979). It would be more difficult for the standard view to accommodate the possibility that an organism could exhibit a qualitatively distinct morphological phenotype, generated by an alternative developmental pathway, which could not be rationalized as the product of incremental natural selection.

An example such as amphibian metamorphosis, in which more than one morphological phenotype is associated with a given genotype, and the transition between the two is triggered by an environmental input, would not impress a neo-Darwinist as an instance of nonprogrammed, "material"-based morphological plasticity of the sort hypothesized above. Larval and adult forms could justifiably be interpreted as distinct morphological adaptations, evolved as separate genetic programs through selection acting at different stages of the organism's life cycle (Stearns 2000). The environmental control of sexual anatomy in reptiles (Deeming and Ferguson 1988) is similarly laden with adaptive considerations. The following three examples, however, one from a fungal species and the other two from vertebrates, provide evidence for significant morphological plasticity for which scenarios of emergence by independent, incremental evolution of alternative genetic programs are highly implausible.

(i) *Candida albicans*, a frequent fungal pathogen in humans, is able to switch among forms ranging from single budding cells, to threadlike hyphae, to strings of yeast-like cells plus long septated filaments, known as pseudohyphae. The organism's morphology varies with

its environment: in rich media ellipsoidal single cells predominate, whereas pseudohyphae form in response to starvation and other conditions (Braun and Johnson 1997; Ishii *et al* 1997). The general transcriptional repressor *TUP1* is required to maintain the single-celled yeast form. When both copies of this gene are deleted the organism grows exclusive as pseudohyphae (Braun and Johnson 1997). (Paradoxically, deletion of *TUP1* in a different yeast, *S. cerevisiae*, depresses pseudohypha formation; Magee 1997.) The fact that in the absence of the *TUP1* gene product the genes for pseudohypha formation are constitutively active has led to the suggestion that rather than being a yeast that can assume various forms, *C. albicans* actually has no "default" morphology (Magee 1997).

TUP1 is not the exclusive genetic mediator of the yeast-pseudohypha transition in *C. albicans*. Disruption of all active copies of the gene for Rbf1, another transcriptional factor, led to pseudohyphal growth on all media tested (Ishii *et al* 1997; Aoki *et al* 1998).

These examples illustrate the principle that an organism may exhibit multiple viable morphological phenotypes that can be selectively elicited in different environments. As long as an environment persists, the organism's inherited morphology will be the one characteristic of that setting. Alteration of a gene, or establishment of a new link in a genetic network, can cause one of the inherent morphologies to appear regardless of environmental setting.

(ii) McLaren and Michie (1958) studied two inbred strains of mice with different predominant numbers of lumbar vertebrae: the *C*3*H* strain (5 lumbar vertebrae) and the *C*57*BL* strain (6 lumbar vertebrae). It had previously been found that in reciprocal crosses between these strains the maternal strain's characteristic number dominated over that of the paternal strain in the offspring (Green and Russell 1951). To distinguish between mechanisms for this maternal effect involving characteristics of the egg, on the one hand, or of the uterine environment, on the other, the investigators performed reciprocal crosses, but transferred some of the *C*3*H* × *C*57*BL* embryos to the uteri of *C*57*BL* females. They found that whereas the "normal" *C*3*H* × *C*57*BL* hybrids had predominantly 5 lumbar vertebrae, like the maternal strain, the transferred *C*3*H* × *C*57*BL* hybrids had predominantly 6 lumbar vertebrae, like the gestational mothers. The uterine environment therefore had a major effect on a key developmental patterning process.

This example permits us to infer that even in modern vertebrates with highly determinate and canalized development, morphogenetic processes are sufficiently plastic to be capable of being systematically rerouted by non-genetic influences. To take this one step further, one might say that morphogenesis of the segmental plate under standard conditions is a plastic, material process with alternative morphogenetic outcomes which are determined in nontrivial ways by specific external parameters. Clearly allelic variations can tune these parameters so that the outcome is biased in one direction or another, but the functions of the genes involved would only be decipherable in relation to the generic processes that they modulate.

(iii) Domesticated mammals exhibit a number of common transformations with respect to their feral counterparts despite having arisen from different taxonomic orders (e.g. dogs, cattle, pigs, goats) and having been domesticated at different times and places. The mid-twentieth century Russian geneticist D K Belyaev, building on Darwin's observations in the "Origin of Species", took note of the fact that all or most domesticated varieties gave rise to individuals with floppy ears, piebald coat colour, and wavy or curly hair. None of these features appear in wild varieties (with the sole exception of floppy ears in elephants). Craniofacial proportions also change: domesticated dogs, for example, have shorter, broader snouts than wolves.

As noted by Belyaev, if the domestication process had simply been based on selection for, and disruptive of, gene complexes underlying quantitative traits, then the incidental characters unrelated to socialization, such as those listed above, would have been different in populations harbouring different mutations. On the contrary, mammals of both the same and different orders, "domesticated by different people in different parts of the world, appear to have passed through the same morphological and physiological evolutionary pathways" (Trut 1999).

Belyaev and his colleagues performed breeding experiments on captive, farmed (but not domesticated) silver foxes (*Vulpus vulpus*), a species that had never been domesticated before. Their only selection criterion was docility. Nonetheless, they found that within a small number of generations, foxes appeared with piebald colouration, floppy ears, shorter, wider snouts, altered craniofacial proportions, and a significantly later onset of the "fear response" – the same changes that had occurred throughout the history of domestication in other, unrelated lineages.

Belyaev and his colleagues proposed a common explanation for these effects in terms of epigenetic influences analogous to those described above in the lumbar vertebrae study. In docile mothers the gestational environment of the embryo contains decreased levels of aggression- and stress-associated hormones. This affects embryonic development in a variety of ways. For example, the *Star* gene, which is tied to the expression of piebald colouration, slows down the migration of neural crest-derived melanoblasts in fox embryos, causing them to arrive at some epidermal destinations an average of two

days later than wild type melanoblasts (Prasolova and Trut 1993). But *Star* gene functional state is transmitted by epigenetic mechanisms. It appears in (outbred) fox populations undergoing domestication with a frequency greatly exceeding that expected for new mutations, and appears to be inherited as a "paramutation" (Hollick *et al* 1997), elicited in some way by the gestational environment provided by tame mothers (Belyaev *et al* 1981). A summary of this work can be found in Trut (1999).

These results suggest that covert morphological plasticity with no evident adaptive rationale has common "directional" properties across a wide range of mammalian orders. Most significantly, they also provide evidence for an epigenetic route of intergenerational transmission of morphological change: since animals gestated in an environment with low levels of stress hormones themselves exhibit lower levels of such hormones during their own reproductive cycles, altered endocrine status and any of its other developmental sequelae will persist in these subpopulations. These alterations, of course, will also provide raw material for classic stabilizing selection.

5. Conclusion

In attempting to understand developmental mechanisms in contemporary metazoan organisms we are strictly limited to experiments on, and comparisons between, living forms which are all products of the more than half a billion years of evolution that has transpired since the dawn of multicellularity in the Precambrian (Conway Morris 1993). During that period, in each extant lineage, old genes have persisted, have been duplicated and mutated, have entered into new relationships to one another, and have been recruited to new functions. New genes have arisen and have undergone similar transformations. It is generally agreed that body plans and other major morphological motifs of the metazoa were established in the early Cambrian (perhaps 530 mya) (Gould 1989; Conway Morris 2000), with perhaps a few embellishments in the succeeding 1–200 million years, such as the vertebrate limb (Coates 1994). The changing roles of genes against this relatively constant morphological landscape makes it inconceivable that the complex genetic circuitry observed, and perturbed, in developmental studies of modern organisms can constitute functional machinery for the production of organismal forms in the same sense that CPUs and RAM chips are functional machinery for computers, or cylinders and drive trains are functional machinery for automobiles.

Despite increasing recognition that genetic networks have been "rewired" over the course of evolution (Szathmary 2001; Wray 2001), that "key" genes can often be knocked out of complex organisms with little or no phenotypic consequence (Shastry 1995), and that the same genetic manipulation may give rise to animals exhibiting profoundly different phenotypes when present on diverse genetic backgrounds (Sigmund 2000), the typical study in the most rigorously reviewed developmental biological journals still bears a title such as "*Gene X* is essential for avian lung morphogenesis" or "Ectopic expression of the *Y* gene inhibits gastrulation in *Xenopus*". Few of these papers attempt to put the genes they study in their proper context by considering the global (including generic, physical) nature of the morphogenetic process in which the genes participate, or any evolutionary scenarios for the entry of the gene into the morphogenetic mix.

Indeed, the culture of basic biological research is still so genetically determinist that the author of a review of a recent report that a transcription factor gene is mutated in a family with a severe speech and language disorder (Lai *et al* 2001) found it necessary to state that this nevertheless did not appear to be "the distinctively human 'gene for language' that the linguists dream of" (Bishop 2002).

In the absence of a theory for origination of morphological traits other than mutation-based incremental trial-and-error, there is no alternative but to reject the idea of rapid, large scale organizational innovations, and search for functional significance in every molecular detail. This is the "reverse-engineering" approach that dominates contemporary developmental biology. But if, as seems likely, organisms were originally Proteus-like, subject to molding by externally-conditioned, self-organizing, epigenetic processes, subsequent molecular evolution would have had primarily restricting, consolidating, and reinforcing roles. Deconstructing modern development would thus require testing hypotheses about originating processes and evolutionary trajectories and not confine itself solely to contemporaneous functional analysis.

It is time, then, to put genes in their place. Organisms cannot exist without them, and we certainly cannot neglect their functions in dissecting any biological phenomenon, particularly those involving heredity or development. But to imagine that genes are, or always have been, the dominating causal agent in the evolutionary or developmental generation of organismal form, is to misrepresent them and distort our attempts to comprehend living processes.

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