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Commentary

Evolution in the light of developmental and cell biology, and *vice versa*

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Some recent insights from cell and developmental biology (1) are of special interest to evolutionary biologists. Here, I highlight a few of them, which are selected for reasons best understood by beginning with a short history of current ideas.

Some of the oldest controversies in evolutionary biology stem from disagreement over the origins of adaptive design. Should design be attributed to selection, as Darwin (2) argued, or to development as maintained by Bateson (3)? Gradualism played a crucial role in Darwin's argument because it showed the power of selection to mold complex traits from small variations. The large variants sometimes produced by development, on the other hand, invite explanation of adaptive form in terms of accident or divine creation. Darwin was uncompromising on this point and cleverly explained developmentally mediated heterochrony as involving complex traits first established by gradual change in ancestral juveniles or adults (2, p. 138).

The Darwinian theory of natural selection, firmly wed to gradualism, was reinforced and promoted by the Modern Evolutionary Synthesis (sometimes called the Neo-Darwinian Synthesis), which emphasized the importance of small genetically mediated variations for evolutionary change within populations. A side effect of the synthesis was a further downplaying of development, in part because it continued to be identified with saltation and antiselection arguments, e.g., in the work of Goldschmidt (4) and others (see refs. 5 and 6 for more thorough discussions), and because attention focused strongly and profitably on the genetic causes of variation (7). In genetic experiments, variability that was associated with flexibility and condition-sensitive development came to be regarded as noise, a factor to be controlled and not studied for its own sake.

Recently, there has been an upsurge of interest in phenotypic plasticity and development in relation to evolution and a feeling that a Second Evolutionary Synthesis is in store, which will include development alongside genetics as a factor in evolutionary change (8). Many of the first major book-length efforts along these lines during the past fifteen years (e.g., see refs. 6 and 9–15) have come from developmental biologists taking an integrated, comparative approach to ontogeny, genetics, and phenotype organization rather than from biologists originally working in evolutionary biology (but see refs. 16–21). Developmental biologists, taken broadly to include some embryologists, molecular biologists, cell biologists, endocrinologists, neurobiologists, and developmental psychologists, study the construction of phenotypes—the observable properties of molecules, embryos, organs, cells, and behaviors. Phenotype development is well known to be influenced, but not completely determined, by genes. The great potential importance of developmental studies for evolutionary biology is that these studies can illuminate how the variable and condition-sensitive phenotypes of organisms, termed by Lewontin (22) "the real stuff of evolution," are related via specific mechanisms to genes, the elements that enable phenotypes to evolve. Kirschner and Gerhart (1) illustrate how flexible development, rather than being an alternative to selection in the evolution of form, mediates the production of selectable variation. They propose that environmentally sensitive flexibility, far from just interfering with the effects of genes, can ameliorate the deleterious results of mutation and of environmentally induced variation, increasing the viability of novel forms.

Evolvability is the ability of particular features of systems to facilitate change. Already common in computational sciences and discussions of artificial life, this term recently has begun to appear in journals of genetics and evolutionary biology (e.g., refs. 23 and 24). These discussions emphasize genetic aspects of evolvability, defining it as "the genome's ability to produce adaptive variants when acted upon by the genetic system" (24) or as "equal to the heritability of a trait times the square root of the additive genetic variance of that trait divided by the population mean of the trait" (23, 25). A new dimension is given to this concept by Kirschner and Gerhart (1), who define evolvability as "the capacity to generate nonlethal phenotypic variation" thereby giving more emphasis to the phenotype and its development than do earlier definitions. They show how versatile mechanisms of development and flexibility permit smooth functioning of cellular processes and viable developmental change, in spite of the inevitable and sometimes extreme variations imposed by different genotypes and environmental factors. They go on to suggest that these same mechanisms could facilitate *evolutionary* change, and, when this is the case, such mechanisms also might be favored by selection at the level of the clade or lineage, enhancing the diversity and survival of taxa that possess them.

Kirschner and Gerhart approach things from an angle that may be new for biologists who are interested in the adaptive evolution of traits; rather than viewing conserved features as having been selected primarily for efficient function and a specific optimal design, they point out that some key, highly conserved developmental mechanisms are characterized by not being programmed for a particular specialized job and in some cases by profligate inefficiency. Instead of depicting interactive processes as highly coevolved, finely tuned, and irrevocably interconnected, they see the processes as often potentially independent and versatile in the ability to participate in different associations, not tied to a particular task but easily shuffled and recombined among many.

Kirschner and Gerhart (1) use examples from their own fields, cell biology and experimental embryology. They treat only multicellular animals (Metazoa) and only the small number of species that have been studied in detail. How generally acceptable are their conclusions, especially those that have to do with evolutionary biology, which like any other highly specialized subculture of science has its own language and sacred cows and aspires to invent principles of transformation applicable to all forms of life?

The properties of flexible mechanisms that Kirschner and Gerhart (1) consider important for evolvability are compartmentation, redundancy, robustness, weak linkage, and exploratory behavior. These features certainly are not confined to the

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cells and embryos of a few species of animals. There is reason to think that compartmentation, e.g., is a universal property of phenotypes. Sometimes called "modularity," compartmentation refers to the hierarchical division of phenotypes into subunits controlled by switches (e.g., refs. 6, 14, 26, and 27). Because morphological development is extensively if not universally mediated by binary switches (14), modularity was recognized early as a feature of morphology (28). Phenotypic modularity is implied by the familiar word "trait." Although there may be shared elements and genetic correlations among traits, these are relatively discrete aspects of phenotypes. Switch-controlled modules characterize the organization of protein domains, behavioral alternatives, physiological responses, life-history traits, and the organization of animal societies as well (27, 29–32).

Modular dissociability, or the propensity for independent variation and shuffling of structural traits during evolution, has been noted in embryology (28), molecular biology (33), and paleontology (34). Vermeij (34) identified the evolutionary versatility of a lineage with the number of independently variable components of its phenotype. Nevertheless, Kirschner and Gerhart (1) have some new things to say about modularity, all the more important in view of the generality of modular organization. Their concept of "weak linkage," for example, refers to the ability of phenotypic modules to interact in different combinations. This concept draws attention to a point (35) previously overlooked in discussions of modularity and combinatorial evolution: modules that are developmentally recombined must be not only dissociable but also able to function and respond in many contexts, rather than being so precisely tailored that they are effective in only one.

Functional redundancy is a familiar consequence of gene duplication, which by producing multiple copies allows for divergence of function. Kirschner and Gerhart extend the concept to properties of cells and embryos. The concept can be extended further, to a large array of alternative phenotypes at all levels of organization, in both plants and animals (27, 36) with the same evolutionary buffering effect of redundancy and evolved divergence—a feature of evolutionary innovation termed by Darwin (2) "duplication of function." The qualities of what Kirschner and Gerhart call "exploratory systems" include phenomena sometimes labeled somatic selection and self-organization that involve the seemingly wasteful overproduction of variants, followed by persistence, multiplication, or repetition ("selection") of those appropriately located, rewarded, or used. Kirschner and Gerhart show that exploratory systems include a broader class of phenomena than previously appreciated, such as the behavior of microtubules involved in mitotic spindle formation and other phenomena familiar to all biologists but not usually seen as hypervariable mechanisms of flexibility, whose widespread occurrence in nature may be attributable to their ability to accommodate variation and change. Although a term like "somatic selection" draws attention to the fact that some variants become fixed or stabilized during development, the concept of exploratory systems draws attention to the flexibility afforded by multiple alternative potential solutions. It also invites the extension of this insight to examples outside of embryology and above the cell level, to such phenomena as search behavior of animals (37), the search-like movements of growing plants that Darwin (38) called "circumnutation," and even trial and error learning (see ref. 15 for other examples).

Taken together, this confluence of evidence from different fields suggests that the phenomena discussed by Kirschner and Gerhart do not stand as isolated special cases but are part of a larger and more coherent picture of flexible phenotype structure. Their view of developmental mechanisms as not just organizing devices but as sources of flexibility that enhance evolvability are likely to have broad application within biology.

The evolutionary implications of a phenotypic definition of evolvability require special attention. Kirschner and Gerhart (1) believe that "mutational change is needed for phenotypic change" in evolution, and they describe flexible mechanisms of reorganization and accommodation that ". . . must reduce the number of random mutational steps" needed for specific changes to occur. In fact, their line of reasoning, followed to its logical conclusion, reduces the number of mutations necessary for an episode of adaptive evolution to zero. If condition-sensitive, flexible development is the generator of selectable variation, as they maintain, then environmental conditions and side effects of change in other contexts, as well as mutation, can induce novel traits. An example is the inverted dorsal–ventral organization of the chordate phylotypic stage compared with that of arthropods, which Kirschner and Gerhart describe as a response to change in orientation with respect to gravity (1). Missing from their argument is some explanation of how selection on novel *phenotypic* variants can cause evolution, defined as involving gene frequency change. A solution is readily available in the form of genetic variation, which is found in virtually all populations in which genetic polymorphism has been investigated and in the related fact that virtually any phenotypic trait subjected to artificial selection shows a response to selection (22, 40). Although mutation is the ultimate source of this variation, mutation need not be associated with the origin of a particular phenotypic novelty.

Because of this potential for *genetic accommodation*—adjustment of the frequency of occurrence of a phenotypic trait due to selection on genetic variation in the polygenic regulatory mechanisms influencing its threshold of expression—a phenotypic theory of evolvability like that proposed by Kirschner and Gerhart is eminently compatible with the modern theory of evolution by gradual quantitative genetic change. The mechanisms of flexibility they discuss contribute to *phenotypic accommodation*—nongenetic adjustment among interacting, somewhat independently variable parts of an organism, due to phenotypic plasticity. General consequences of phenotypic accommodation are to promote organismic function in spite of inevitable variations because of genetic and environmental causes and to facilitate evolution by accommodation of novel traits (1, 15, 27).

The kinds of mechanisms discussed by Kirschner and Gerhart help to correct certain misconceptions suggested by some evolutionary discussions that would surprise most developmental biologists. The opinion is sometimes expressed, for example, that mechanisms of phenotypic plasticity are poorly understood (41) or that plasticity *per se* (which would include the clearly adaptive mechanisms discussed here) may not evolve under natural selection, currently a controversial point (42).

The idea of evolution of evolvability—that the ability to evolve can itself evolve—might be questioned by some evolutionary biologists because it requires selection above the individual level. Adaptive evolution, however, concerns the genetically mediated spread of traits within populations, species, or clades (39). Several evolutionary biologists (e.g., 24, 43) have argued cogently in favor of clade selection for evolvability with reference to genetic aspects. The mechanisms of flexibility discussed by Kirschner and Gerhart seem to be especially good candidates for clade-level selection because the mechanisms can become established within species due to the immediate, individual advantages of flexibility and then be favored secondarily at higher levels (see ref. 44) because of their contributions to speciation, diversification, and major (macroevolutionary) change (27, 36). Darwin (2) was the first to argue in favor of selection for variability *per se* as part of his "principle of divergence," which included the idea that processes that contribute to intraspecific diversification also would enhance the differential survival and multiplication of descendent clades.

The unification of flexible mechanisms with a genetic theory of evolution helps to eliminate the old tendency to oppose development and selection as mutually exclusive architects of form. Selection cannot generate form, and development cannot cause a fitness-enhancing form to increase in frequency within a population. Development, with its built-in flexible responsiveness to both gene products and environment, is responsible for the *origin* of viable, selectable phenotypic variation, as Kirschner and Gerhart argue, whereas selection explains which variants then spread and are maintained. So evolution is always a two-step process, involving first developmentally mediated variation and then selection resulting in gene frequency change.

There is still a discernible difference between developmental *evolutionary* biology and evolutionary *developmental* biology. In the preface to their book "Cells, Embryos and Evolution," for example, Gerhart and Kirschner (15) cite with approval Dobzhansky's famous dictum, "Nothing in biology makes sense except in the light of evolution." Then they speculate that, "Today Dobzhansky might be tempted to say, 'Nothing in evolution makes sense except in the light of cell biology.' " Even though Dobzhansky was a geneticist, however, he ended his version of that phrase with "evolution," not "genetics." If Dobzhansky had read the Kirschner and Gerhart (1) *Perspective* on evolution, flexibility, embryos, and cells, I suspect that he would have considered it ample confirmation of his original words.

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