How Do Precise Adaptive Features Arise in Development? Examples with Evolution of Context-Specific Sex Ratios and Perfect Beaks

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PERSPECTIVES IN ORNITHOLOGY

HOW DO PRECISE ADAPTIVE FEATURES ARISE IN DEVELOPMENT? EXAMPLES WITH EVOLUTION OF CONTEXT-SPECIFIC SEX RATIOS AND PERFECT BEAKS

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The older writers on evolution were often staggered by the seeming necessity of accounting for the evolution of fine details, for example, the fine structure of all the bones. From the view that structure is never inherited as such, but merely as types of adaptive cell behavior which leads to particular types of structure under particular conditions, the difficulty to a considerable extent disappears. (Sewall Wright 1931:147).

ARE GENERATIVE PROCESSES CAUSES OR CONSEQUENCES OF EVOLUTION?

ORGANISMAL BIOLOGISTS ARE lucky to have in front of them, in the field or in the laboratory, an ever-present proving ground for theories that seek to explain the daunting diversity and complexity of the biological world. Foremost among these is the origin and evolution of precise adaptations that we observe around us. We are taught that evolution of these adaptations is accomplished by natural selection, and indeed there is good evidence that once an adaptive modification arises in a sufficient proportion of the population, natural selection acting on its heritable determinants becomes a powerful force for its evolutionary spread, establishment, and further modification. But where do actual adaptive solutions initially come from? How do selectively advantageous traits arise during development?

It is intuitively clear that many of the precise and complex behaviors, functions, and patterns that we see around us are largely emergent—that is, not "determined" in a conventional population-genetics sense. It is naive to talk about genetic determination and adaptive evolution of every minute element of composite behaviors involved in the complex aerial display of a hummingbird, the coordinated dance sequence of manikins, the integration of neurological and biomechanical mechanisms that enable a swallow to skim the water surface in flight, or the ontogeny of complex camouflage in a sandpiper chick. Even the simplest of these phenomena involves precise coordination of millions of neurons and biochemical pathways, and there are simply not enough genes to specify every step

and combination of these elements, much less their evolutionary retention. But even if there were billions of available genes for determination of these elements and of their context-dependent combinations, the population-genetics requirements for origination of such specification by natural selection (e.g., Crow and Kimura 1970, Gavrilets 2004, Lynch 2007, Lynch and Abegg 2010)—incremental fitness increases of intermediate (and not yet functional) stages, significant genetic penetrance of most elements, and very large population sizes—are unrealistic for most complex adaptations and organisms that we study and certainly impossible in any bird species. Yet these complex functions, patterns, and behaviors are precise; are repeatable within species, lineages, and families; and, thus, bear all the marks of evolutionary stability that we typically associate with genetic determination. Clearly, some other solutions are needed to explain their origins, and the search for these solutions could not be timelier.

Recent discoveries have established extraordinary conservation of basic molecular and cellular mechanisms over vast phylogenetic distances and organismal systems (e.g., Davidson 2006, Koonin and Wolf 2009, Shubin et al. 2009). For example, the evolution of the overwhelming majority of molecular and cellular mechanisms that generate contemporary adaptations in birds preceded not only the evolution of animals, but also the origin of multicellularity (Newman 2006, King et al. 2008). Furthermore, the speed with which complex adaptations appear (e.g., multiple origins of flight morphology within vertebrates) is difficult to reconcile with gradual accumulation of incremental steps, but is concordant with heritable changes in regulatory rearrangements of conserved developmental and functional modules (Müller and Newman 2003, Kirschner and Gerhart 2005, Reid 2007). Although current functional use and adaptive significance do not provide particularly deep insights into evolutionary origin and developmental causes (e.g., Gould and Lewontin 1979), much contemporary thinking in ornithology assumes that they do.

Our tendency to merge natural selection—the process arising from variation in the fit between members of a population and their environment—with the process of development is traceable

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to historical simplification of Darwin's (1859) original view of natural selection as the driver of both local adaptation and evolutionary diversification—the view that assumed direct inheritance of adaptive modifications and, thus, explicitly merged selection and development, such that selection shapes developmental variation that it subsequently sorts. Although Darwin famously considered developmental variation "slight, random, and abundant," which was necessary for giving natural selection a creative role in evolution, less known is the fact that Darwin also excluded natural selection from processes that generate novelty, because natural selection, in his view, could act only on what is already common and established (Gould 2002, Reid 2007).

Regardless of the reasons, confounding natural selection and developmental variation necessarily forces us to neglect generative processes in evolution and the fact that behind every morphological, physiological, and behavioral change is a modification of the organisms's development, and exploratory and emergent processes play a defining role in this process (Baldwin 1902, Johnston and Gottlieb 1990, West-Eberhard 2003, Forgacs and Newman 2005, Kirschner and Gerhart 2005, Badyaev 2011). Indeed, remarkable conservation of generative processes over evolutionary time not only brings forth the question of how natural selection can accomplish tremendous phenotypic diversity with such a limited set of ingredients, but, most importantly, gives us a powerful insight into how evolutionary change actually proceeds. The central emerging theme is that autonomous developmental processes can create configurations that strongly reduce the number of evolutionary steps needed for the evolution of precise and novel adaptations and can also greatly facilitate their evolutionary retention. Consequently, novelties, diversification, and adaptation are best understood in terms of conserved developmental processes being stabilized and arranged by natural selection (Whyte 1965, Callebaut et al. 2007).

DISTINGUISHING ADAPTATION FROM ADAPTABILITY

Evolution proceeds by combining conserved and modular generative processes into hierarchical configurations at different times, places, and contexts by regulatory changes (King and Wilson 1975, Gould 1977, Alberch 1980, Stern 2000, Wilkins 2001, Carroll 2005, Davidson 2006, Gerhart and Kirschner 2007). These regulatory elements are subject to genetic changes and evolutionary fixation. However, because their core components are unchanging and do not deplete their phenotypic variability, evolution of such adaptive configurations does not preclude subsequent diversification and modification.

Explicit focus on the mechanisms that give rise to phenotypes brings forth the realization that the processes arising from fundamental biochemical and physical properties of biological tissues and their interaction with the environment provide the very basis for innovations, exploratory behaviors, and developmental plasticity (Forgacs and Newman 2005, Kicheva et al. 2007, Montell 2008, Newman 2010, Haigo and Bilder 2011) that can subsequently be exploited and stabilized by genetic drift and natural selection. Evolved plasticity and adaptability of these autonomous core processes greatly facilitate evolution because they account for initial environmental response, population spread, and epigenetic integration of novel adaptive solutions (Baldwin 1902, Schmalhausen 1938)—steps that are needed for eventual evolution of genetic integration. Whether prolonged periods of epigenetic integration of

novel traits in a population are followed by their genetic integration depends on the consistency of natural selection, and, in many cases, epigenetic integration is a transient and reversible stage that, for example, enables populations to become established in novel environments. Regardless, this view calls for explicit separation of processes that produce adaptations from processes that maintain and modify them and, thus, lifts the burden of creativity from natural selection and places it on the functioning and developing phenotype (e.g., Piersma and van Gils 2010). In this framework, natural selection provides "boundary conditions" for developmental variability (West-Eberhard 2003, Müller 2007, Badyaev 2011) and can facilitate innovation by the mobilization and stabilization of core developmental components that are not themselves targets of selection.

Here, I suggest that decoupling natural selection and development gives powerful insights into the phenomenon of coexistence of precise adaptations—something that is assumed to be formed by natural selection by consistently eliminating developmental variability—and exceptional diversification in the same traits, implying an abundance of developmental variability that does not interfere with adaptive evolution. Such perspective removes two major stumbling blocks in understanding the evolution of complex adaptations. First is the necessity to account for incremental fitness increases of intermediate stages of complex (and yet not functional) features. Second is the necessity to account for coordinated evolution of every minute element of complex adaptation—something that commonly results in unrealistic expectations of evolutionary rates and population sizes.

The key to applying this perspective is to understand the nature of phenotypic variation that arises during development, and I illustrate it here with two particularly puzzling empirical phenomena in avian biology—the evolution of context-dependent adjustments of sex ratio in relation to laying order of eggs in a clutch and coexistence of precise adaptation and exceptional diversification in beaks. I show that the common resolution of both phenomena lies in the decoupling of natural selection and core developmental processes and the realization that both are guided by evolution of regulatory changes that determine the time, context, and congregation of conserved generative processes—organization that enables precise local adaptation as well as extensive diversification.

COMPLEX EGG-LAYING ORDERS: RECONCILING ADAPTIVE ADVANTAGE AND RARITY OF CONTEXT

The precision and speed with which sex bias in the laying order of eggs is expressed in appropriate environmental contexts is puzzling. For a trait as complex as sex-biased egg-laying order, this expression seems to require an improbable combination of coordinated evolutionary changes in follicle sequestration order, growth, ovulation, and sex-determination. Evolution of such a multistep adaptation would require unusually strong and persistent selection (i.e., a single predominant context) over many generations. Yet adaptive sex-biased egg-laying orders are commonly expressed in response to rare and variable contexts such as mate quality, seasonal changes, resource abundance, and population establishment (Ankney 1982, Cordero et al. 2001, Velando et al. 2002, Andersson et al. 2003, Duckworth 2009).

Resolution of this paradox lies in the realization that the self-regulatory and emergent processes that govern the dynamics of
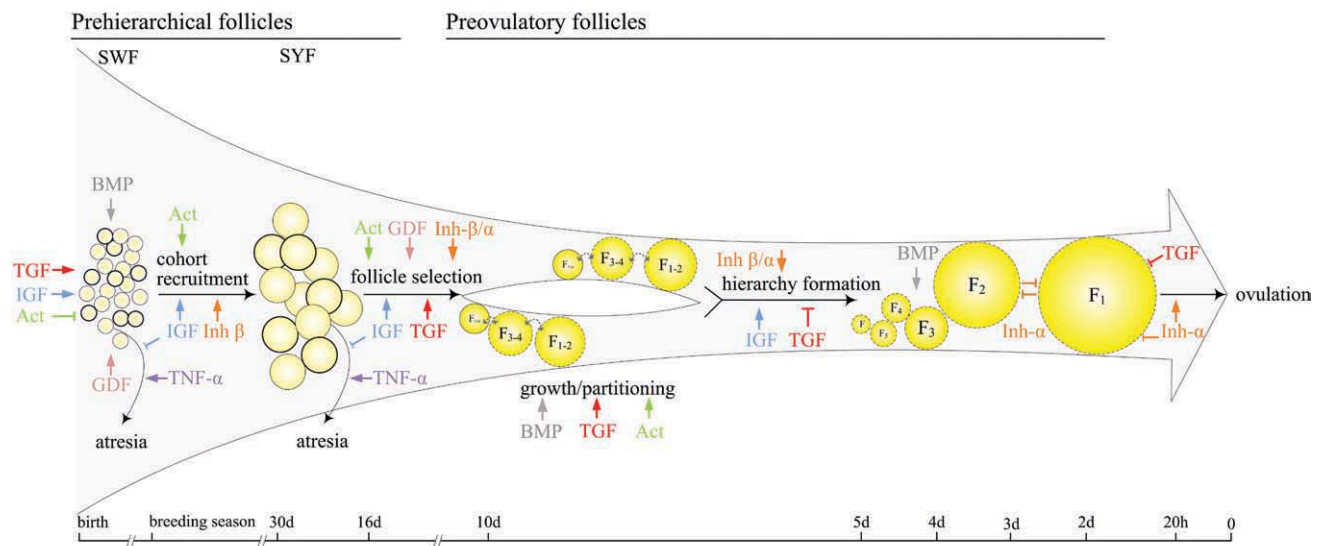
Clutch size	$\uparrow$IGF, Inh-β/α	$\uparrow$TGF, IGF, Inh-β	$\uparrow$IGF	$\uparrow$ Inh-β/α	$\uparrow$ Inh-α	$\uparrow$Inh-α
Ovulation order/ clustering	$\uparrow$Act, Inh-β/α		$\uparrow$Act, TGF	$\uparrow$ Inh-β/α	$\uparrow$ Inh-α	
Sex-determination	$\uparrow$	$\uparrow$	$\uparrow$		$\uparrow$	
Steroid gradient	$\uparrow$		$\uparrow$		$\uparrow$	
Lipid/vitamin gradient			$\uparrow$		$\uparrow$	

FIG. 1. Main growth factors producing context-specific modulation of organism-wide signaling of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Growth factors are transforming growth factor-β (TFG), insulin-line growth factor (IGF), tumor necrosis factor-α (TNF-α), bone morphogenetic proteins (BMP), inhibin-α (Inh-α), inhibin-β (Inh-β), Inh-β/Inh-α ratio, and activin (Act). Time scale is calibrated for the House Finch (*Carpodacus mexicanus*). At the onset of breeding season, cohorts of small white follicles (SWF) are advanced to the small yellow follicle (SYF) stage; the order of recruitment is linked to initial acquisition of the ability to transport yolk across membranes. Differences in timing of consecutive SYF selections into preovulatory groups can result in groups that initiated growth at different times in relation to their hormonal synthesis and exposure to plasma hormones. Follicles in such necessarily heterochronic groups grow rapidly, partition (double-headed arrows) liver-produced yolk precursors with adjacent follicles in their groups, and eventually merge into a common ovulatory hierarchy guided by disproportional growth and associated spatial effects of inhibin-signaling by the largest follicle (F1). The LH surge that causes F1 to ovulate simultaneously stops growth of F2 and advances it to ovulation stage. Table shows developmental stage and growth factors (when known) that were shown to regulate adaptive changes in clutch size, ovulation order, sex determination, and egg-laying-substance gradients (based on Moreau et al. 1998, Hoffman et al. 2007, Badyaev et al. 2008a, Rutkowska and Badyaev 2008, Onagbesan et al. 2009).

oogenesis in birds (Fig. 1) can produce nonrandom coordination of oocyte growth, ovulation order, and sex determination under routine perturbations of shared physiological mechanisms. In this case, the role of natural selection is limited to discrimination among the combinations of oocytes produced by developmental processes and, if context is persistent enough, to fine tuning regulation of a favored configuration so that it can be reliably produced in the future. Ubiquitous reuse of the same regulatory elements throughout oogenesis (Fig. 1) gives natural selection only a few targets, but these targets can accomplish an entire array of changes in sex determination and egg-laying order that can be produced essentially instantaneously and without major genetic changes in conserved core processes of oogenesis.

During the breeding season, the avian ovary contains three main classes of oocytes: small white follicles (SWF) that have been present in the ovary since embryonic stage, small yellow follicles (SYF) that are produced by periodic recruitment of cohorts of SWF with the onset of breeding season, and rapidly growing preovulatory oocytes that are selected from a few SYF, form a pronounced size hierarchy and ovulate sequentially during egg laying (Fig. 1). All types of follicles are present in the ovary at the same time, and all aspects of their recruitment, atresia, growth, and interactions are regulated at the organismal level by two key pituitary gonadotropins (FSH and LH; Fig. 1). However, although all oocytes, irrespective of stage, are exposed to the same hormonal surges, several highly conserved signaling elements (growth factors) convert these surges

into context-specific effects on follicle development (Fig. 1; Johnson 1996, 2000; Johnson et al. 1996; Woods and Johnson 2005; Onagbesan et al. 2009). For example, in preovulatory follicles, the effect of FSH on activin produces oocyte membrane gaps that enable yolk uptake and facilitate follicular recruitment (Schuster et al. 2004), whereas in the older follicles activin modulates FSH receptor sensitivity and regulates growth (Chen and Johnson 1996, Johnson et al. 2008). Similarly, in prehierarchical follicles inhibin prevents follicular differentiation, whereas at the preovulatory stage it produces a regular ovulation rate (Lovell et al. 2001, 2003; Yang et al. 2001; Johnson et al. 2005). Depending on location within the ovary, TGF (Fig. 1) modulates the same LH signaling to (1) prevent SWF atresia, (2) increase growth and prevent over-recruitment of SYF (thus regulating clutch size), (3) keep preovulatory follicles alive, and (4) advance follicles in the ovulation sequence (Fig. 1; Johnson and Woods 2009, Onagbesan et al. 2009).

Such redundancy and conservation, along with pronounced emergent properties of oogenesis—such as the hierarchy produced by disproportionate growth, self-organization of hierarchical clusters, and activation–inhibition of within-ovary arrangements of preovulatory oocytes (Badyaev et al. 2006b, Lebedev et al. 2006, Tosca et al. 2006)—mean that only a few regulatory changes can accomplish strong and reversible coordination of ovulation order, sex determination, and allocation of substances in oocytes (Fig. 1), resulting in repeatable complex egg-laying orders in response to environmental or physiological conditions experienced by breeding females. Such effects can be maintained epigenetically for a prolonged time and be expressed in an entire population without acquiring genetic determination (Uller and Badyaev 2009)—and most probably they never do, because selection favoring such complex egg-laying patterns is unlikely to be recurrent over multiple generations. The role of natural selection is thus limited to eliminating "nonsurvivable" combinations of ovulation order, sex determination, and substance allocation (e.g., female sex bias in oocytes with greater testosterone allocation) and retaining favorable combinations under recurrent conditions (e.g., male bias in clutches produced by malnourished mothers). Importantly, selection does not "cause" these complex sex-biased egg-laying patterns, but only sorts and stabilizes emergent sex-biased oocyte configurations.

Our studies of House Finches (*Carpodacus mexicanus*) provide strong support for this scenario: we documented close integration of oogenesis, intra-ovary oocyte dynamics, and sex-determination under common endocrinological mechanisms that regulate female reproduction and homeostasis. House Finches show strong, complex, and reversible sex bias in egg-laying patterns in response to novel environments and stressors (Badyaev et al. 2003, 2006a), patterns that appear rapidly and spread widely in newly established populations, but that are not expressed (although they are inducible) in native populations (Badyaev and Oh 2008). Although these patterns were key in the establishment of House Finches across their recently expanded range, they do not appear to involve genetic change in regulatory elements, but instead capitalize on emergent integration of ovulation order, sex bias, and steroidogenesis under physiological mechanisms that regulate female homeostatic response to environmental change (Badyaev 2009). This scenario is likely more common than is currently realized and could plausibly account for frequently documented, but evolutionary elusive, context dependency in sex-biased ovulation order in birds.

AVIAN BEAKS: RECONCILING ADAPTATION AND DIVERSIFICATION

Avian beaks are some of the best-studied examples of both precise adaptation and extreme evolutionary diversification. Evolution of such adaptations requires both close genetic integration of beak components and high heritability of their development to produce the incremental fine tuning of beak morphology. However, such consistent elimination of developmental variability should, at the same time, prevent the evolutionary diversification of beaks that is commonly observed in birds (Grant 1986, Benkman 1993, Lovette et al. 2002).

Resolution of this paradox lies in the realization that many of the emergent and self-regulatory processes that constitute beak ontogeny (Fig. 2) are not themselves visible to natural selection. Instead, the role of selection is largely confined to eliminating and stabilizing postproduction configurations of conserved developmental modules and to fine tuning such configurations to the most recurrent context. Ubiquitous reuse of conserved regulatory elements throughout beak ontogeny (Fig. 2) gives selection an opportunity to rapidly accomplish adaptation, within-species polymorphism, and evolutionary diversification (Fig. 2) without depletion of developmental variability or excessive waiting time and population sizes needed for incremental evolution of complex beaks.

Beak morphogenesis starts with migration of neural crest cells into the embryo's facial region and mandibular arch (Fig. 2; Helms and Schneider 2003). Neural crest cells retain their stem cell characteristics during migration and do not have an affinity for a final placement until they arrive at their final destination and aggregate into five facial prominences that will ultimately merge into a beak (Fig. 2). The induction and transport of neural crest cells is regulated by a protein gradient (Fig. 2), and once cells form prominences they become enclosed by an ectoderm-derived layer of epithelium (Helms and Schneider 2003, Wu et al. 2006, Geetha-Loganathan et al. 2009). Activation–inhibition interactions and compensatory growth of rapidly dividing mesodermal cells in adjacent prominences and their ectodermal envelopes determine the juxtaposition of prominences and delineate the placement of a future beak (Fig. 2). Continuing cell proliferation induces reciprocal regulatory feedback between the mesenchyme cells and epithelium boundaries within each prominence, with the epithelium layer providing bounding effects and axial orientation directing cell outgrowth (Wu et al. 2006, Eames and Schneider 2008, Hu and Marcucio 2009). Rapidly growing frontonasal, two lateral nasal, and two maxillary prominences (Fig. 2) then merge and, bounded and directed by activation–inhibition feedback from their epithelium layer, form the upper beak. Merging of two mandible prominences produces the lower beak (Fig. 2). The prominences and their signaling networks are notoriously modular, autonomous, and conserved—they can be surgically divided and doubled-up within an embryo (e.g., producing shoveler-like beaks in chickens), or transferred between species (e.g., producing chimeric "qucks" [ducks with quail bills] and "duails" [quails with duck beaks]), or even exchanged between mouse and chicken (reviewed in Eames and Schneider 2005, Jheon and Schneider 2009).

In later embryonic stages, interactions between proliferating cartilage and bone areas of the upper beak activate local factors (Fig. 2) fine tune beak length and curvature, with many shapes emerging as a straightforward geometric consequence of cell proliferation and juxtraposition and the ratio of cartilage to bone cell mass
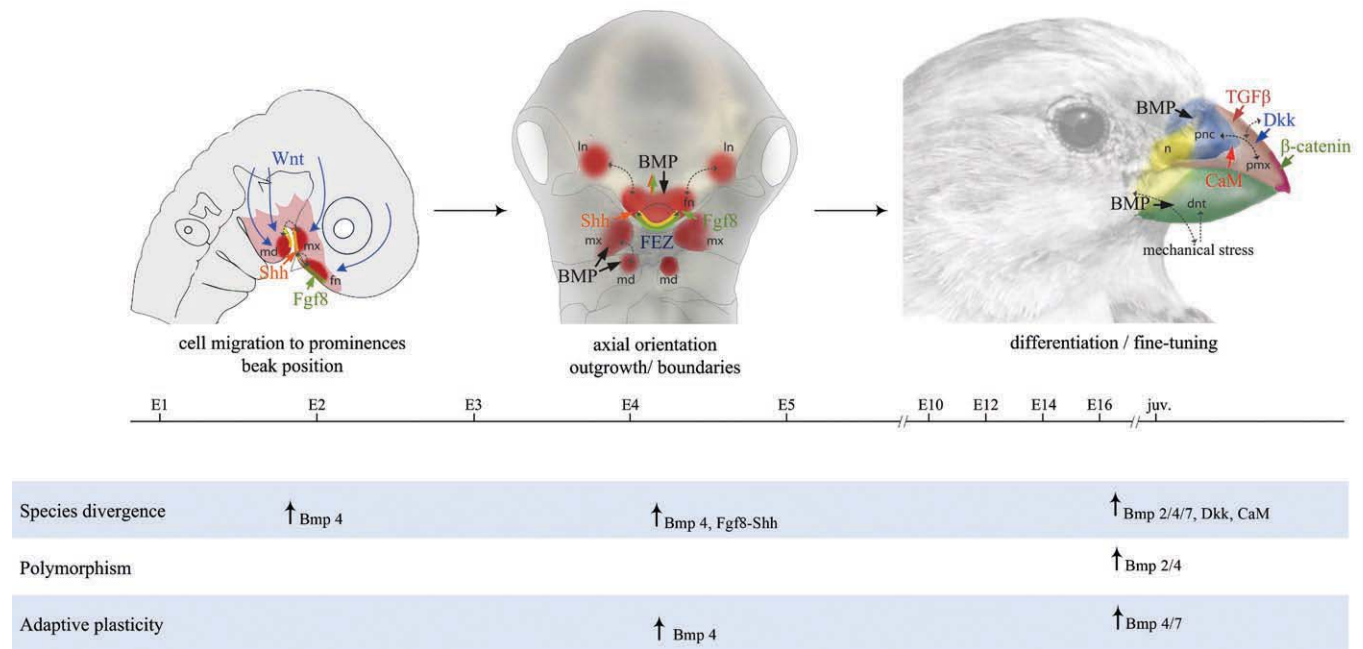
Fig. 2. Main growth factors, organizational principles, and modular structure of beak morphogenesis. Groups of growth factors are wingless type (Wnt), fibroblast growth factor 8 (Fgf8), sonic hedgehog (Shh), bone morphogenetic proteins (BMP), transforming growth factor beta (TGFβ), calmodulin (CaM), Dickkopf (Dkk), and β-catenin. Time scale is based on the House Finch (hatching on days 12–14), but is broadly conserved across birds. Facial prominences (shown in red), formed by aggregation and proliferation of neural crest cells, are frontonasal (fn), lateral nasal (ln), mandibular (md), and maxillary (mx). Cartilage and bone areas arising during late development in beak are prenasal cartilage (pnc), premaxillary bone (pmx), nasal bone (n), and dentary bone (dnt). Double-headed arrows show interactions between neighboring prominences during growth and expansion (left and middle figure), tissue partitioning between pnc and pmx, and effects of mechanical stress conductance in late developmental stages (right figure). Left figure: migrating neural crest cells (blue arrows) aggregate in prominences, and interaction between Shh and Fgf8 domains determines the beak placement (dashed triangle). Middle figure (frontal view of an embryo): ectoderm (green) and mesoderm (yellow) layers in fn show major regulatory effect of the frontonasal ectodermal zone (FEZ) on Bmp regulation of cell proliferation. Right figure: Bmp and CaM are expressed in different parts of pnc affecting mostly beak depth and length correspondingly. Tissue tradeoffs between pnc and pmx zones regulate Dkk effect on beak length. Table shows developmental stage and growth factors that were shown to regulate species divergence, polymorphism, and adaptive plasticity in beak size and shape (based on Abzhanov et al. 2004, 2006; Wu et al. 2004, 2006; Helms and Brugmann 2007; Badyaev et al. 2008b; Clabaut et al. 2009).

(Wu et al. 2006, Abzhanov et al. 2007, Campàs et al. 2010, Mallarino et al. 2011). In later nestling and juvenile stages, mechanical stress associated with muscle attachment and force leads to local production of Bmp and further fine tuning of functional beaks (reviewed in Young and Badyaev 2007). The entire process is regulated by conserved regulatory factors that have distinct effects depending on the time and place of their expression. For example, Bmp 4 regulates distinct processes at different times (Fig. 2)—early commitment of neural crest cells to bone formation (Abzhanov et al. 2007), later cell proliferation within prominences (Wu et al. 2004), species-specific outgrowth of cartilage–bone areas in the upper beak (Abzhanov et al. 2004), mechanical stress-induced bone formation in both the upper and the lower beak, and adaptive plasticity in beak size between habitats (Badyaev et al. 2008b).

The evolutionary significance of such modular organization and conserved signaling is that only a few genetic changes in regulatory elements can facilitate rapid evolution of local adaptation and extensive evolutionary diversification without depletion of genetic variance in beak morphology. Under this scenario, the role of natural selection is limited to eliminating developmental abnormalities and to stabilizing developmental configurations most adaptive under prevalent conditions. Genetic fixation of mutations in regulatory elements can enable evolutionary persistence of most favored configurations, but redundancy of the regulatory network, compensatory interactions among its elements, and overall highly modular organization assures short-term evolutionary retention of many functional configurations of beaks.

This scenario is corroborated by developmental and genetic changes in beak morphology that accompanied evolution of locally adapted beaks over 19 consecutive generations following colonization of a novel environment by the House Finch (Badyaev 2010). We found rapid reorganization and exceptional diversity in beak morphologies followed by reversible microevolutionary changes in the first few generations. Adaptive equivalence of distinct beak configurations enabled survival of House Finches in novel environments and wide exploration of beak morphospace before the most appropriate beak configuration was found and stabilized. The role of directional selection during this period was

Table 1. General predictions of phenotypic changes during adaptive evolution under two scenarios.

If core developmental processes are independent from selection…	If selection guides basic development…
(1) Rapid reorganizations and abrupt microevolutionary changes	(1) Gradual and continuous microevolutionary change
(2) Adaptive equivalence of distinct configurations	(2) Retention and improvement of an optimal configuration
(3) Regulatory components are main targets of heritable change in a composite structure	(3) Incremental coordinated changes in all developmental components of a composite structure

largely confined to elimination of developmental extremes and abnormalities produced by compensatory developmental interactions among beak components, while the beak's genetic architecture mirrored long-term stabilizing selection, assuring retention of adaptive evolutionary change (Badyaev 2010). Importantly, compensatory adjustments among beak components shielded genetic variance in individual traits, enabling production of locally adaptive morphology without compromising future modifications. That such rapid phenotypic evolution of local adaptation can be accomplished in only a few generations and in a small founder population of a few thousand birds (making natural selection too weak a force to directly modify developmental organization of beaks) is a testament to the evolutionary potential of such developmental organization (Fig. 2; Badyaev 2010).

Taken together, the examples with oocytes and beaks illustrate the general principle that redeployment and combinatorial changes in conserved developmental modules (that are not themselves a subject to natural selection) in a new place, time, and context in ontogeny enables evolution of adaptation by natural selection. This perspective provides a nonconventional, but perhaps more biologically realistic, set of evolutionary predictions (Table 1) that might be particularly relevant to the study of systems such as birds, in which an overwhelming majority of adaptations is produced by rearrangements of core processes that evolved billions of years ago in a completely different context. Most importantly, these examples are a powerful reminder that explicit conceptual separation of processes of origination and adaptation—that is, taking the concept of natural selection out of the process of development—along with detailed understanding of the developmental dynamics of adaptive traits that we study in the field invariably provides crucial insights into many outstanding problems in empirical evolutionary biology.

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