SPECIAL ARTICLES

The functional matrix hypothesis revisited. 4. The epigenetic antithesis and the resolving synthesis

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In two interrelated articles, the current revision of the functional matrix hypothesis extends to a reconsideration of the relative roles of genomic and of epigenetic processes and mechanisms in the regulation (control, causation) of craniofacial growth and development. The dialectical method was chosen to analyze this matter, because it explicitly provides for the fuller presentation of a genomic thesis, an epigenetic antithesis, and a resolving synthesis. The later two are presented here, where the synthesis suggests that both genomic and epigenetic factors are necessary causes, that neither alone is also a sufficient cause, and that only the two, interacting together, furnish both the necessary and sufficient cause(s) of ontogenesis. This article also provides a comprehensive bibliography that introduces the several new, and still evolving, disciplines that may provide alternative viewpoints capable of resolving this continuing controversy; repetition of the present theoretical bases for the arguments on both sides of these questions seems nonproductive. In their place, it is suggested that the group of disciplines, broadly termed Complexity, would most likely amply repay deeper consideration and application in the study of ontogenesis. (Am J Orthod Dentofac Orthop 1997;112:410-7.)

"It is a fallacy that the genome, the totality of DNA molecules, is the main repository for developmental information; i.e. that there exists a genetic program, or blueprint, theoretically capable of creating an entire organism."[98]

Biological Mechanisms and Processes Defined

This article continues the dialectical analysis of the roles of genomic and epigenetic processes and mechanisms in the control of craniofacial growth and development. Previously a genomic thesis was outlined and several critical terms were defined.[99] The dialectic process concludes here with an epigenetic antithesis and a resolving synthesis, following two additional definitions: (1) A process is a series of actions or operations that lead toward a particular result. (2) A mechanism is the fundamental physical or chemical process(es) involved in, or responsible for, an action, reaction, or other natural phenomenon.[100] That is, mechanisms underlie processes. For example, loading a femur is an epigenetic process: the possible resultant modification(s) of bone cell DNA (for example by methylation[101,102]), or of chondrocytic DNA (for example as reflected in differential regulation of biosyntheticic pathways[103]), are epigenetic mechanisms. Similarly, the specific steps of the activation and deactivation of appropriate portions of the bone cell genome, associated with the trio of possible osteoblastic responses to loading (deposition, resorption, or maintenance of bone tissue) are further examples of epigenetic mechanisms that control the genome. In this sense, the original versions of the functional matrix hypothesis (FMH) described only epigenetic processes,[4-8] whereas recent revisions also described epigenetic mechanisms.[9,10] The fundamental correctness of earlier FMH descriptions is supported by more recent research.[104,105]

The Epigenetic Antithesis

Some of the principal strengths of this antithesis come from precise definitions of what a gene is and is not. For example: (a) "gene. The unit of heredity: one or more nucleic acid sequences incorporating information necessary for the generation of a particular peptide or RNA product"[106]; and, (b) "enough is known about the genetic machinery . . . [to know] . . . that this is virtually the only kind of information which polynuceotide molecules are inherently capable of containing: nothing there

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0889-5406/97/$5.00 + 0 **8/1/79951**

at all about which proteins will be expressed in which cells at what time and in what quantities."[98]

The genomic thesis is denied because it is both reductionist and molecular; that is, descriptions of the causation (control, regulation) of all hierarchically higher and structurally more complex morphogenetic processes are reduced to explanations of mechanisms at the molecular (DNA) level. For example, the genomic thesis of craniofacial ontogenesis passes directly from molecules to morphogenesis: directly from DNA molecules to adult gross morphology, ignoring the role(s) of the many epigenetic processes and mechanisms competent to control (regulate, cause) the large number of intervening, and increasingly more structurally complex, developmental stages[13,18] particularly, and there are additional similarly reductionist views of odontogenesis.[17,22,60,107,108]

The epigenetic antithesis, detailing both processes and mechanisms, is integrative,[109] seeking to clarify the causal chain between genome and phenotype. Its goal is to identify and describe comprehensively the series of initiating biological processes and their related underlying (biochemical, biophysical) responsive mechanisms that are effective at each hierarchical level of increasing structural and operational complexity.[110]

This article reviews some of the clinically significant epigenetic processes and mechanisms, existing at several organizational (structural, functional) levels, that regulate (direct, control, cause) cephalic and craniofacial (musculo-) skeletal morphogenesis.

Craniofacial Epigenetics

"Broadly speaking, epigenetics refers to the entire series of interactions among cells and cell products which leads to morphogenesis and differentiation. Thus all cranial development is epigenetic, by definition." This view is supported here,[15,19,20,111] despite continued expressions of genomic regulation of craniofacial morphogenesis.[13,14]

As previously noted,[99] epigenetic factors include (1) all of the extrinsic, extraorganismal, macroenvironmental factors impinging on vital structures (for example, food, light, temperature), including mechanical loadings and electromagnetic fields, and (2) all of the intrinsic, intraorganismal, biophysical, biomechanical, biochemical, and bioelectric microenvironmental events occuring on, in, and between individual cells, extracellular materials, and cells and extracellular substances.

In terms of clinical orthodontics, and of the FMH, all therapy is applied epigenetics, and all appliances (and most other therapies) act as prosthetic functional matrices. Clinical therapeutics includes a number of epigenetic processes, whose prior operations evoke a number of corresponding epigenetic mechanisms. These latter, in turn, underlie the observed processes of tissue adaptations by both skeletal units and functional matrices.

Epigenetic Processes and Mechanisms

In craniofacial morphogenesis, more is known presently about processes than about mechanisms. Despite this, it is no longer sufficient to note, for example, that otherwise undescribed epigenetic processes of "intrauterine environment" can regulate fetal mandibular growth.[112] The future aim must be to elucidate the molecular, genomic, mechanisms[101] whose activation underlies the adaptive growth processes of the mandibular functional cranial components (that is, of the mandibular skeletal units and their related functional matrices).

Loading

Many different epigenetic processes can evoke mechanisms capable of modifying DNA.[113-116] At clinically significant structural levels, physical loading is unquestionably of the greatest importance. "Among the numerous epigenetic factors influencing the vertebrate face is mechanical loading."[118] It is useful to consider the epigenetic process of loading and some of the epigenetic mechanisms this process evokes.

Loading per se. Loads may be imposed at many structural levels. While clinical observations usually are macroscopic, the loadings act microscopically, at molecular and/or cellular levels.[117] Loadings are able to regulate several alternative molecular (cellular) synthetic pathways (mechanisms) of many tissues, including bone[118]; for example, the mechanical environment is important in maintaining the differentiated phenotype of bone cells.[102] It should be noted that loading may be dynamic (for example, muscle contraction) or static (that is, gravity); and to be effective, loads may increase, decrease, or remain constant.

Mechanical loading is known to influence gene expression.[119,120] Of clinical (and FMH) interest, extrinsic musculoskeletal loading can rapidly change (1) both articular cartilage intercellular molecular syntheses[121] and mineralization[122]; and (2) osteoblastic (skeletal unit) gene expression.[123,124] Epigenetic loading processes include gravitational variations that evoke unique mechanisms of molecular synthesis.[125]

Extracellular matrix deformation. Musculoskeletal tissue loading inevitably deforms an extracellular matrix (ECM) that is not developmentally inert. Rather, in several ways, ECM regulates the formation, development, and maintenance of its included cells that synthesize the ECM.[126-129] Further, ECM can regulate multicellular tissue morphogenesis[130] and contribute to genomic regulation of its enclosed cells.[131]

Cell-shape changes. Tissue loading can also alter cell shape. This inevitably deforms intracellular constitutents, in cluding the cytoskeleton.[132-134] The epigenetic process of changing cell shape invokes the epigenetic mechanisms of mechanotransduction of biophysical forces into genomic and morphogenetically regulatory signals.[135-138]

Cell-shape change processes can also activate several other epigenetic mechanisms, for example, stretch-activated ion channels in cartilage and other mechanically initiated cell-signaling mechanisms.[139-142] There is recent orthodontic interest in the cell-shape change of nonskeletal cells.[143]

Cell-shape change may lead to nuclear shape deformation. This, in turn, is a mechanism that can directly cause (regulate) a consequent alteration of the mechanisms of genomic activity.[140]

Epigenetic cell signalling processes. Several loading processes can regulate genomic expression. One, previously described, begins with cellular mechanoreception and mechanotransduction of the loading stimulus into an intercellular signal that undergoes parallel processing within a connected cellular network of bone cells.[9,10] The details of cell-signalling are reviewed extensively elsewhere.[144]

Chains of intracellular molecular levers. A second epigenetic cellular process begins with deformation of the ECM. This matrix has an epigenetic regulatory role in morphogenesis, by virtue of integrin molecules that physically interconnect the several molecular components of the intracellular (cytoskeletal) and the extracellular environment (for cartilage).[145,127,128,146-148] While the form (size and shape) of the cytoskeleton may be physically controlled by a broad spectrum of loadings,[133,149] it responds identically to all.[150]

The epigenetic mechanism evoked consists of a physical array of intracellular macromolecular chains, acting as levers, extending from the cell membrane to multiple specific sites on each chromosome.[146] The molecular chain acts as an information transfer system between the extracellular environment and the genome, transmitting signals generated by deformations of the ECM directly to the intranuclear genome.[9,10] Indeed, such informational transfer between cells and ECM is dynamic, reciprocal, and continuous.[151]

Other processes and mechanisms. (1) DNA methylation is a potent epigenetic event. It is involved in many intracellular, extracellular, and intercellular mechanisms.[101] It can "introduce novel features of cellular function far removed from the classical Mendelian view of the gene, chromosome, and inheritance . . . with information flowing back to the DNA level and changing gene expression,"[152,153] the genome now being considered as a sophisticated response system and a carrier of information,[154] a system activated by several epigenetic processes and mechanisms.[155] (2) There are numerous examples of yet other processes and mechanisms of epigenetic regulation of the genome.[113,115,156-159] (3) In addition, it has been shown that (botanical) epigenetic factors can impose metastable inheritable changes in the plant genome,[160-163] a nontrivial matter not considered further here.

Epigenetic Regulation of Higher Structural Levels

In addition to the molecular and cellular processes and mechanisms noted, over a century ago the discipline of developmental mechanics (entwicklingsmechanik)[85,86] established that the epigenetic process of extrinsic loadings play a major role in the regulation of bone tissue and bone organ growth, development, and morphology.[118,164-167]

At the tissue level, there are several causal, strain-specific differences in bone tissue microstructure.[168-171] Closely similar epigenetic mechanisms and processes are observed in the adaptational responses of all connective tissues, including cartilage, to loading.[164,165,172-175]

At the organ level, the ability of the processes of motion and of articular function to regulate joint morphology is well-known[176-178]; and, of course, physical activity processes regulate oganismal skeletal adapational responses.[179] Other epigenetic processes affecting bone tissue include local vascular factors.[180]

Regulation of functional matrices. Periosteal functional matrices are under closely similar epigenetic control. Mechanical loads regulate skeletal muscle (periosteal functional matrix) phenotype[181]; and chronic muscle stimulation can change its phenotype.[182-184] Numermous studies establish the neurotrophic role of neural innervation in muscle genome regulation.[185-188] It remains only to note the truism that, for muscle as for bone, mechanical epigenetic factors, broadly termed function (or ex-

ercise) significantly control musculoskeletal growth, development,[187,189,190] and maintenance of structural and physiological attributes.[191-193]

A Resolving Synthesis

"It seemed that the next minute they would discover a solution. Yet it was clear to both of them that the end was still far, far off, and that the hardest and most complicated part was only just beginning."—*Anton Chekov. The Lady with the Dog.*

As the epigraph indicates, it is certain that no matter what arguments, theoretical constructs, and supporting experimental data are presented here, the prevailing tension between the genomic thesis and epigenetic antithesis will continue unabated. Nevertheless, a resolving synthesis will at least clarify the bases for continued discourse.

The fundamental argument of this resolving synthesis, based on an analysis of casuation, was presented earlier,[11] and later amplified.[99] It argues that morphogenesis is regulated (controlled, caused) by the activity of both genomic and epigenetic processes and mechanisms. Both are necessary causes; neither alone are sufficient causes; and only their integrated activities provides the necessary and sufficient causes of growth and development. Genomic factors are considered as intrinsic and prior causes; epigenetic factors are considered as extrinsic and proximate causes. The data supporting this synthesis are provided here and above.[99]

It is acknowledged that the validity of this dialetic synthesis is significantly dependent on the validity of its epigenetic antithesis. In turn, a defensible epigenetic antithesis should convincingly suggest some process(es) and/or mechanism(s) that can regulate (direct, control, cause) morphogenesis. It is argued here that these are provided by the newly emerging disciplines of complexity.

Complexity and self-organization

The theories of ontogeny and phylogeny currently are being significantly reinvigorated by the new and evolving science(s) of complexity that integrate topics from mathematics (for example, cellular automata, fractals, strange attractors), biology (for example, genetic algorithms, artificial life simulations, neural networks, emergence, adaptive systems, connectivity), and physics, while minimizing distinctions between them. Complexity theory (CT) also integrates specifically related topics in bioengineering and the computer sciences; for example, chaos, information, and hierarchical theories, fuzzy logic, as well as cyto(tissue)mechanics and molecular (nano)mechanics.[194-212]

Because epigenetic processes and mechanisms are best explained as examples of CT, a clearcut demonstration of the role of CT in craniofacial ontogeny, at some point, is both necessary and possible. But in this place only this brief, intuitive preview is possible. Because fairness to both the novelty and conceptual richness of CT requires a comprehensive presentation to make it generally intelligible, it will be substantively reviewed subsequently.

CT provides descriptions of the behavior of complex biological systems that exist as "ensembles" of several tissues and organs, and not as clusters of individual cells and extracellular substances. Such an ensemble (identical to a functional cranial component in the FMH) is termed here as a complex adaptive system (CAS), structurally arrayed as a vital continuum. This term is defined here as it is in the several analytical finite element methods (FEM) recently introduced into orthodontics and physical anthropology.[213-221]

CT provides compact, statistical descriptions of the collective growth behavior of such CAS continuity. During ontogeny, vital CAS exhibits the creation of robust, spontaneous, and emergent order.

An algorithm for control of such a CAS requires that it is able to alter itself in response to the (epigenetic) information produced by the system it is trying to control. In a CAS, minor changes in the epigenetic input can cause huge fluctuations in the morphological output.

CT, as it utilized information theory, assumed that a CAS processes information (both genomic and epigenetic) in a parallel, not a serial, manner.[10] Where most previous biological theories of development were based on the methods of deterministic (genomically predetermined), classical mechanics, information theory, and CT, are probabilistic (epigenetically self-organized and emergent), and are based on the methods of statistical mechanics. It is probable that ontogeny involves nonlinear processes and is not fully predictable; that is, growth and development, to a significant extent, exhibit both random behaviors and frequent perturbations. To clarify this point, note that previously most biological models were studied as if they were linear. That is, when their mathematical formulas were graphed they looked like straight lines. Linear systems are predictable: the calculus shows the changes in their state, and statistics (especially regression analysis) reduces their data to a line. However, CT makes it clear that most biological systems are nonlinear and are not most correctly described by these mathematical techniques; nonlinear formulations are necessary.

The highly ordered morphological properties of adult complex biological systems (for example, functional matrices and skeletal units) result from the operation of a series of spontaneous and self-organized ontogenetic processes and mechanisms.[194,200] Such emergent self-organizing events can create phenotypic variability under constant genetic and other extraorganisaml epigenetic conditions.[222]

The operation of complexity can be suggested as follows. "Environmental factors thus play a decisive role in all ontogenetic processes. But it is the organism itself that, as an integrated system, dictates the nature of each and every developmental response . . . the living organism self-organizes on the basis of its own internal structuring, in continuous interaction with the environment in which it finds itself."[113]

CONCLUSIONS

Integration of pertinent advances in biomedical and bioengineering permitted an ongoing revision of the functional matrix hypothesis. The first two articles in this series, by emphasizing the roles of a number of biophysical and biochemical factors in the regulation of morphogenesis, implicitly argued for the correctness of the fundamentally epigenetic thrust of the FMH. However, because the conceptual tension between hypotheses suggesting the regulatory primacy of either genomic (genetic) or of epigenetic factors and/or processes in morphogenesis continues unabated, it seemed useful to reevaluate this nontrivial matter, using the dialectical method of presenting a thesis, an antithesis, and a resolving synthesis as illustrated in these two interrelated articles.

I believe that the most appropriate conclusion permitted by the data bases at this time is to use the contemporary managerial phrase . . . "it is a win-win situation." Again, using a popular phrase, genomic and epigenetic processes are "apples and pears" More correctly, they are examples of totally differing types of causation—genomic formal cause and epigenetic efficient cause. Individually both are necessary causes, but neither are sufficient causes alone. Together they provide both the necessary and sufficient causes for the control (regulation) of morphogenesis. Nevertheless, epigenetic processes and events are the immediately proximate causes of development, and as such they are the primary agencies. The fuller demonstration of exactly how epigenetic events carry out their roles will be considered elsewhere in the context of a review of the implications of complexity theory for the functional matrix hypothesis.

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