The functional matrix hypothesis revisited. 2. The role of an osseous connected cellular network

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Intercellular gap junctions permit bone cells to intercellularly transmit, and subsequently process, periosteal functional matrix information, after its initial intracellular mechanotransduction. In addition, gap junctions, as electrical synapses, underlie the organization of bone tissue as a connected cellular network, and the fact that all bone adaptation processes are multicellular. The structural and operational characteristics of such biologic networks are outlined and their specific bone cell attributes described. Specifically, bone is "tuned" to the precise frequencies of skeletal muscle activity. The inclusion of the concepts and databases that are related to the intracellular and intercellular bone cell mechanisms and processes of mechanotransduction and the organization of bone as a biologic connected cellular network permit revision of the functional matrix hypothesis, which offers an explanatory chain, extending from the epigenetic event of muscle contraction hierarchically downward to the regulation of the bone cell genome. (Am J Orthod Dentofac Orthop 1997;112:221-6.)

The first article in this series considered the implications for the functional matrix hypothesis (FMH) of the ability of bone cells to carry out intracellular mechanosensation and transduction and intercellular communication. In this article, we will consider the implications for the FMH of the inclusion of connectionist network theory.

BONE AS AN OSSEOUS CONNECTED CELLULAR NETWORK (CCN)

All bone cells, except osteoclasts, are extensively interconnected by gap junctions[87-91] that form an osseous CCN.[7,8,42] In these junctions, connexin 43 is the major protein.[92] Each osteocyte, enclosed within its mineralized lacuna, has many ($n = \pm 80$) cytoplasmic (canalicular) processes, ± 15 μm long and arrayed three-dimensionally, that interconnect with similar processes of up to 12 neighboring cells. These processes lie within mineralized bone matrix channels (canaliculi). The small space between the cell process plasma membrane and the canalicular wall is filled macromolecular complexes.

Gap junctions are found where the plasma membranes of a pair of markedly overlapping canalicular processes meet.[93] In compact bone, the canaliculi cross "cement lines," and they form extensive communications between osteons and interstitial regions.[94] Gap junctions also connect superficial osteocytes to periosteal and endosteal osteoblasts. All osteoblasts are similarly interconnected laterally. Vertically, gap junctions connect periosteal osteoblasts with preosteoblastic cells, and these, in turn, are similarly interconnected.[95] Effectively, each CCN is a true syncytium.[87,91,93] Bone cells are electrically active.[57,58,85,95-101] In a very real sense, bone tissue is "hard-wired."[7,8,96]

In addition to permitting the intercellular transmission of ions and small molecules, gap junctions exhibit both electrical and fluorescent dye transmission.[63] Gap junctions are electrical synapses, in contradistinction to interneuronal, chemical synapses, and, significantly, they permit bidirectional signal traffic, e.g., biochemical, ionic.

Mechanotransductively activated bone cells, e.g., osteocytes, can initiate membrane action potentials capable of transmission through interconnecting gap junctions. The primacy of ionic signals rather than secondary messengers is suggested here, because, although bone cell transduction may also produce small biochemical molecules that can pass through gap junctions, the time-course of mechanosensory processes is believed to be too rapid for the involvement of secondary messengers.[25,32] (See Carvalho et al.[102] for an opposite view.) A CCN is operationally analogous to an "artificial neural network," in which

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massively parallel or parallel-distributed signal processing occurs.[103-105] It computationally processes, in a multiprocessor network mode, the intercellular *signals* created by an electrical type of mechanotransduction of periosteal functional matrix *stimuli*. Subsequently the computed network output informational signals move hierarchically "upward" to regulate the skeletal unit adaptational *responses* of the osteoblasts.

Fortunately, the bases of connectionist theory are sufficiently secure to permit modeling of a biologically realistic osseous CCN.[106-110] It consists of a number of relatively simple, densely interconnected processing elements (bone cells), with many more interconnections than cells. It is useful that bone cells form a network because individual receptors cannot code unambiguously-only a population of cells can do so.[103]

In network theory, these cells are organized into "layers": an initial input, a final output, and one or more intermediate or "hidden" layers. Importantly, such networks need not be numerically complex to be operationally complex.[111] The operational processes are identical, in principle, for all bone cells in all layers. Regardless of the actual physiological stipulatory process, each cell in any layer may simultaneously receive several "weighted" inputs (stimuli). A weight is some quantitative attribute. In the initial layer, these represent the loadings. Within each cell independently, ". . . all the weighted inputs are then summed."[112] This sum is then compared, within the cell, against some liminal or threshold value. If this value is exceeded, an intracellular signal is generated, i.e., successful mechanotransduction occurs. This signal is then transmitted *identically* to all the "hidden" layer cells (adjacent osteocytes) to which each initial layer cell is connected by gap junctions (and there are many styles of connectivity). Next, similar processes of weighted signal summation, comparison, and transmission occur in these intermediate layers until the final layer cells (osteoblasts) are reached. The outputs of these anatomically superficial cells determines the site, rate, direction, magnitude, and duration of the specific adaptive response, i.e., deposition, resorption, and/or maintenance, of each cohort of osteoblasts.[113]

Information is not stored discretely in a CCN, as it is in a conventional, single CPU computer. Rather it is distributed across all or part of the network, and several types of information may be stored simultaneously. The instantaneous state of a CCN is a property of the state of all its cells and of all their connections. Accordingly, the informational representation of CCN is redundant, assuring that the network is fault or error tolerant, i.e, one or several inoperative cells causes little or no noticeable loss in network operations,[112] a matter of useful clinical significance.

The CCNs show oscillation, i.e., iterative reciprocal signaling (feedback) between layers. This attribute enables them to adjustively self-organize. This behavior is related to the fact that biologic CCNs are not preprogrammed; rather they learn by unsupervised or epigenetic "training,"[114] a process probably involving structural or conformational changes in the cytoskeleton.[83] The phenomena of both network "training" and "learning" are related to the suggested effects of the oscillatory nature of their strain history.[115] Accordingly, the structurally more complex network attributes and behavior of a CCN gradually or epigenetically self-organize and emerge during operation. These network attributes are not reducible, i.e., they are neither apparent nor predictable from a prior knowledge of the attributes of individual cells.

Gap junctions, permitting bidirectional flow of information, are the cytological basis for the oscillatory behavior of a CCN. All the osteoblasts of a cohort engaged in an identical adaptation process are interconnected by open gap junctions. The presence of sharp histological discontinuities between cohorts of phenotypically different osteoblasts is related to their ability to close gap junctions at the boundaries between such cohorts, and so prevent the flow of information.[116,117] Informational networks also can transmit inhibitory signals, a significant matter beyond present concerns.[118]

A skeletal CCN displays the following attributes: (1) Developmentally, it is an untrained self-organized, self-adapting and epigenetically regulated system. (2) Operationally, it is a stable, dynamic system that exhibits oscillatory behavior permitting feedback. It operates in a noisy, nonstationary environment, and probably uses useful and necessary inhibitory inputs. (3) Structurally, an osseous CCN is nonmodular, i.e., the variations in its organization permit discrete processing of differential signals. It is this attribute that permits the triad of histologic responses to a unitary loading event.

Certain simplifications exist in this article, as in most of the bone literature. It is assumed that bone cells are organized in only two dimensions, bone loadings occur only at discrete loci, and gradients of strain are not considered. However, biologic reality is otherwise. In a loaded three-dimensional bone volume, gradients of deformation must exist, and

each osteocyte probably senses uniquely different strain properties. Further, it is probable that each osteocyte is potentially able to transmit three different adaptational signals, in three different directions—some stimulatory and some inhibitory. However, these processes have not yet been adequately modeled. *The role of periosteal functional matrices: new insight.*

The morphogenetic primacy of periosteal functional matrices on their skeletal units is consensually accepted. As a muscular demand alters, e.g., myectomy, myotomy, neurectomy, exercise, hypertrophy, hyperplasia, atrophy, augmentation, or repositioning, the triad of active bone growth processes correspondingly adapts the form of its specifically related skeletal unit.

Presently excluding the stimulation of neural afferents in muscle, tendon, and periosteum, extrinsic physical loadings tend to deform bone tissue and to invoke skeletal unit (bone) adaptation responsive processes. A classic example is the regulation of coronoid process form by the temporalis muscle.[119] The tension in the tendon of this contracted muscle, transmitted through intertwined periosteal fibers inserted into subjacent bone, deforms the loaded skeletal unit.[120]

Although some periosteal osteoblasts may be directly stimulated,[121] extant data suggest osteocytic primacy in mechanosensory processes.[122] Anatomically, bone cells are competent mechanoreceptors. Their three-dimensional array of extensive canalicular cell processes is architecturally well-suited to sense deformation of the mineralized matrix.[123]

Although no one mechanical parameter reliably predicts all bone adaptational or remodeling responses,[124] *strain* probably plays the primary role[125-128] and is a competent stimulus.[51] The significant strain attribute may vary with specific conditions.[129] These include: (a) loading category-bone responds best to dynamic rather static loading[54]; (b) frequency-osteocytes may be physiologically "tuned" to the frequencies of muscle function,[130-132] tunings being analogous to those of specialized nonosseous sensory cells,[34,35] e.g., auditory hair cells; and (c) magnitude-relatively small microstrains (μe) (about 10^{-6} mm/mm), and strain magnitudes of 2000 ± 1000 μe, are morphogenetically competent.[55,56,129,133]

Although it is reasonably presumed that mechanosensory processes, of both the ionic and mechanical type, involve the plasma membrane of the osteocytic soma or canalicular processes, the receptive, and subsequent transductive, processes are neither well understood nor consensually agreed on.

Skeletal muscle contraction is a typical periosteal functional matrix loading event,[13,14,16,120,134,135] and frequency is one of its critical parameters. Although the fundamental frequency of contracting muscle is about 2 Hz, other strain-related harmonics of 15 to 40 Hz exist.

These higher-order frequencies, significantly related to bone adaptational responses, are "... present within the [muscle contraction] strain energy spectra regardless of animal or activity *and implicate the dynamics of muscle contraction as the source of this energy band*" (italics mine).[68,132,136] Of particular significance to the FMH is the close similarity of muscle stimulus frequencies to bone tissue response frequencies.

MECHANOTRANSDUCTION: A TENTATIVE SYNTHESIS

The previously mentioned data suggest that the ability of periosteal functional matrices to regulate the adaptive responses of their skeletal units by ionic mechanotransductive processes is related to several factors. These are that (a) normal muscle function strains attached bone tissue intermittently; (b) the dynamics of skeletal muscle contraction fit rather nicely with the energetic requirements for bone cell responsiveness; (c) the range of specific strain-frequency harmonics of muscle dynamics are also those found to be morphogenetically competent (i.e., osteoregulatory); (d) normal skeletal muscle activity produces intraosseous electric fields on the order of extrinsic fields found to be similarly morphogenetic; and, (e) bone cells may be stimulated by two mechanisms-directly by strain-activated plasma membrane channels and indirectly by electrokinentic phenomena.

These factors strongly suggest a rather precise matching of significant operational characteristics between a contracting skeletal muscle stimulus and the ability of loaded bone cells to transduce this into signals capable of regulating their adaptive responses. In a phrase, bone appears to be closely "tuned" to skeletal muscle, i.e., skeletal units are tuned to their periosteal functional matrices.

When both the ionic membrane and the mechanical (molecular lever) transductive processes are conceptually and operationally combined with the data of both electric field effects and of contraction frequency energetics, they provide a logically sufficient biophysical basis of support for the hypothesis of epigenetic regulation of skeletal tissue adaptation.[1,13,16-18,38,129,137]

In reality, it is probable that the ionic (electrical)

and mechanical (molecular lever) transductive processes in osteocytes are neither exhaustive nor mutually exclusive. While using differing intermediate membrane mechanisms or processes, they share a common final common pathway, i.e., they eventually produce signals regulatory of osteoblastic activity. Certainly in the ionic processes, and possibly in the molecular lever system mechanism, the transductive process(es) also cause a transplasma membrane ionic flow(s), creating a signal(s) capable of intercellular transmission to neighboring bone cells through gap junctions,[121] and then subsequent biologic computation in an osseous CCN.

CONCLUSION

Where the original FMH version offered only verbal descriptions of periosteal matrix function and skeletal unit response, the addition to the FMH of the concepts of mechanotransduction and of computational bone biology offers an explanatory chain extending from the epigenetic event of skeletal muscle contraction, hierarchically downward, through the cellular and molecular levels to the bone cell genome, and then upward again, through histologic levels to the event of gross bone form adaptational changes. Analyzing size and shape changes by reference-frame-invariant, finite element methods produces a more comprehensive and integrated description of the totality of the processes of epigenetic regulation of bone form than previously possible.

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