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Strain-related control of bone (re)modeling: objectives, mechanisms and failures

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The strains engendered in bone tissue by functional loading are now widely accepted as providing the controlling stimulus for functional control of bone architecture. While an individual's nutritional and hormonal status may significantly influence the cells responsible for bone modeling and remodeling it is difficult to see how these systemic influences themselves could provide the local, loading-related control necessary to establish and maintain an appropriate balance between architecture and loading at each location throughout the skeleton. Similarly, while neurologically-derived influences on bone cells may affect their susceptibility to various stimuli including strain, it is difficult to envisage how local requirements for adaptive (re)modeling could be controlled from the central nervous system.

The ability to measure local bone strain during functional activity[1], coupled with that of being able to apply controlled loads to specific bones *in vivo*[2], supported by techniques including histology, histomorphometry, immuno-cytochemistry, *in situ* hybridization and finite element analysis allows at least three major questions to be addressed.

What subset of bone cells' total strain-related experience provides a regulatory stimulus to the processes of bone (re)modeling?

It became apparent from early bone loading experiments[2] that the process of adaptive (re)modeling was preferentially responsive to short periods of strain change. This suggested a control process dominated by the "error" signals associated with loading situations to which the bone was not habituated rather than one driven by prolonged exposure to customary loading. Within these short periods of loading high strains[2], high strain rates[3] and interruption of strain cycles with periods of rest[4] all increase a strain regimen's osteogenic potential. The effects of vibration on (re)modeling[5] where strain frequencies are high but strain magnitudes two orders of magnitude lower than those achieved during locomotion may or may not be working through the same "programmes" as those derived from functional levels of strain change.

What are the strain-related objectives of the processes of bone modeling and remodeling?

Most experiments using artificial loading are too short for any adaptive (re)modeling response to be completed and thus allow strains before intervention to be compared with those after adaptation. According to the "mechanostat theory" the strains after adaptation should be the same as those beforehand since the presumed objective of the adaptive (re)modeling process, will have been to change the bone's mass and architecture to re-establish them. However, while experiments have given some insight into the waveform of strain change capable of stimulating the adaptive (re)modeling process practically nothing is known of the subset of the total strain information that constitutes the strain-related objective of adaptation. Thus assuming that bone cells have a "target strain environment" is it fixed genetically, influenced by other features of the individual's physiology, or itself varied according to strain history? Does it relate only to peak strains and if so, peak strains anywhere in the bone or at particular places? Are periods of high strains averaged over time with periods of low strains? Does it relate to actual strain change or to some composite measure of strain change such as strain energy density? What is the effect of strain distribution or strain gradients? Is strain change averaged through-

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out the whole bone or a domain, of bone tissue? If a domain what is its extent in relation to the whole bone? These are all major unknowns of practical significance.

By what mechanisms are the strain-related physical experiences of bone cells converted into the controlling stimuli for adaptive (re)modeling by which strain-related architectural objectives are achieved?

This aspect of bone cells' adaptive responses to strain has received more attention perhaps because it is accessible to a wider group of scientists including cell biologists. It is now well recognized that within a short period of being subjected to strain, or one of its immediate physical derivatives such as fluid flow, bone cells undergo calcium fluxes[6], activate intra-cellular ERK pathways[7,8], produce ATP[9], prostaglandins[10] and nitric oxide[11], activate the Wnt pathway[12], depress sclerostin production[13] and alter the expression of a large number of genes[14].

These early strain-related responses presumably constitute the "processing" of strain-related information necessary to produce the controlling stimulus for adaptive (re)modeling. It is at these stages in the functionally adaptive pathway that the consequences of strain-related events interact with those of the individual's genetic background and their nutritional and hormonal milieu. It is as a result of these competing and complementary processes that the final instruction for (re)modeling is produced.

The most prevalent failure of bones' ability to maintain a structurally competent skeleton is post-menopausal osteoporosis in women and age-related osteoporosis in men. In both conditions, after half a lifetime in which bone architecture has been sufficiently robust to withstand everyday loading without fracture, bone mass declines despite continued physical activity. In men and women, the strongest correlate with the level of bone loss is the level of bioavailable estrogen[15]. Despite this association between ovarian function and bone loss being reproducible in animals it has been hard to pinpoint the mechanism involved.

In our laboratory, we have been greatly interested by the involvement of estrogen receptors in a number of bone cells' early responses to strain. It seems that the presence of the estrogen receptor, with or without ligand, is either necessary for a number of these early strain-related responses, or that it has a profound effect on the rate or effectiveness of the reactions to which it contributes. These interactions occur up and downstream of ERK activation[7,8], associated with translocation of β-catenin to the nucleus[12] and activation of the IGF receptor by its ligand[16]. Since these events are among those responsible for converting the immediate effects of strain change into a coherent stimulus for (re)modelling one would expect absence of the ER to be associated with a reduced adaptive response to loading. This appears to be the case[17].

Over the long term, bones' architecture is matched to their customary loading through the cumulative effect on (re)modelling of individual responses to loading events. Less effective processing of the conservational and potentially osteogenic strain-related stimulus will have the same downstream effect in terms of a controlling stimulus for (re)modelling as disuse. The consequences will also be the same; namely bone loss towards a genetically determined minimum. We hypothesise[18,19] that the structurally inappropriate, estrogen deficiency-related bone loss in postmenopausal women, and ageing men, is due in part to less effective processing of potentially osteogenic strain-related stimulation in osteoblasts and osteocytes due to reduced availability of estrogen receptors associated with low levels of estrogen.

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