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Genetically modified mechanostats: Implications for skeletal competence?

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The recognition that bone structure is optimised in relation to prevailing mechanical conditions was pioneered in the 1890s, with the well-described illustration of the proximal human femur showing the strategic alignment of the bone trabeculae, with the principal stress trajectories. The concept of adaptation of both mass and distribution of bone in response to the magnitude and direction of applied loads became embodied in Wolff's Law.

However, the architecture of bone is a consequence not only of the applied loads, but of the genetic template with superimposed mechanobiological modification. Thus, in a given genetically diverse population, the morphology of the skeleton will also show an inherent diversity. Changes in functional activity, age and predisposition to hormonal changes can all modify the morphology and mechanical competence of the skeleton.

The response of the skeleton to changes in mechanical demand and functional adaptation, has been shown to act as a feedback control system regulated by strain, and mediated through signaling of the bone cell populations. Peak strain magnitudes in a wide range of species during peak physiological activity show marked similarity, elegantly summarized by Rubin et al., despite differences in micro-structure.

The skeletal system responds to cyclical deformation and this response has been studied in a wide range of animal species. Data from these *in vivo* studies have also been used to develop algorithms for computer models to simulate bone modeling and remodeling. Yet to date these computer simu-

lations of bone physiology do not make any assumptions related to the genetic component of the bone morphology or sensitivity to functional adaptation. The strain control feedback mechanism was fundamental to Frost's postulation of a "mechanostat" in bone, with a functional role in optimization of structure.

In many biological scenarios population studies are carried out and mean values and variances used, with the acceptance that biological systems are variable. For instance, studies on micro-crack accumulation as a function of age show an age-related increase, which is an acceptable result. However, closer examination of the individual data points for elderly individuals shows a wide spread of values with some having large accumulations and others having no more than young individuals. The same phenomenon is seen in type IIa muscle fibre type loss as a function of aging, with some young individuals having as low a proportion of these fibres as seen in elderly individuals. Perhaps there is a burning need to understand why such variability occurs, rather than accept it as a given.

The response of bone, both as a tissue and as a structure, to mechanical stimulation now appears to be far more complex and this complexity may result from genetic influences.

Judex et al. 2003 have applied a standard *in vivo* model of controlled changes in the mechanical environment of bone to different genetic strains of mice. The structural architecture of a given bone shows differences between genotypes. Furthermore, the response of the bone to increased mechanical demand also shows significant differences between genetic strains. The system is even more complex, in that sensitivity to a reduction in mechanical input is also different between the genetic strains but not aligned to the genotype-associated differences in sensitivity to increased loading. Recent work by Montgomery on the response of bone to physical exercise in human subjects has shown that there are "responders" and "non-responders" in terms of adaptive changes in bone mass. The lack of an adaptive

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response to this level of increased mechanical demand also appears to be associated with insertion/deletion polymorphisms of the ACE gene. Schiessl has also identified individuals in which increased exercise results in adaptation of muscle mass, but not an increase in bone, potentially a genetically mediated modulation of the mechanostat.

In the literature, there are reports of major differences in the material properties of bone in different genetic strains of mice. Wergedal et al. reported variations as great as 200% between strains. We have examined bone and tendon material properties in the thoroughbred racehorse, and found significant correlations between bone and tendon material strength within individuals. Interestingly, even within this gene pool the

differences between individuals can be 2-3 fold. There appears to be an association between total collagen cross-links and these differences in tissue strength. The control of these matrix properties is the subject of current research.

The implication of the genetically-related variance in bone architecture, and functional adaptation in understanding the complexity of the mechanobiology of the skeleton and its relation to bone repair, implant integration and degenerative conditions such as osteoporosis and osteoarthritis, remain to be determined. In summary, understanding the mechanostat, set points, skeletal architecture and relation to skeletal competence is reaching new and exciting levels of complexity.