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SESSION TIME: 1100 - 1150, Tuesday 24 Oct 2006

Invited Plenary Abstracts
Plenary Lectures 4 - Biomechanics

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Why bones break – the material and structural basis of bone strength and fragility

Mark R. Forwood
School of Biomedical Sciences, The University of Queensland, Brisbane Australia

The propensity to fracture is governed by the ratio of maximum strength of bone and the loads applied to the skeleton during normal activities. The contribution of external loads to reductions in this safety factor cannot be ignored because small increases in loading due to objects carried in front of the body, for example, create disproportionately large joint moments at the vertebral bodies. Bone itself must achieve an adequate safety factor while minimising the energy cost of movement. That is, a trade off between strength and lightness. Cortical bone must also achieve sufficient stiffness to act as an efficient lever, without becoming excessively brittle, a trade off between stiffness and toughness. Cancellous bone is weaker than cortical bone, but more flexible, allowing it to act as an efficient shock absorber. The hierarchical structure of these two forms of bone allows stiffness to be achieved in the former by an architecture that arrests cracks and prevents their propagation (toughness); and in the latter dissipating energy through greater deformation and microdamage, allowing recovery of structure rather than failure and compaction of the shock absorber. The strength and stiffness of bones *per se* depend on the strength and stiffness of their material, and the build of the whole bone structure. This offers three possible mechanisms to reduce their risk of fracture. First, increase bone mass – larger bones can resist greater loads. Second, distribute that mass most effectively – a small addition to bone mass can substantially increase bending and torsional strength if placed strategically. Third, improve the material properties of the bone tissue – make the bone matrix, itself, stronger or capable of absorbing more energy. Adding, or redistributing, bone mass influences structural properties, affecting the behaviour of bones as an organ. Alterations in the bone material are manifested in the mechanical properties of bone per unit volume, reflected in measures of stress, strain, modulus of elasticity and modulus of toughness. The influence of such factors that affect bone fragility, but are not accounted for by bone mass, or quantity, has been termed bone quality. It is argued that these variables explain the disparity between the change in BMD and the reduction in fracture risk in response to treatment. Although they are necessary to understand a bone's risk of fracture, they are more inscrutable than mass to measure in vivo. Such factors include mineral density, maturation and chemical composition; collagen structure and biochemistry; osteocyte viability; tissue microdamage; and, micro-architecture. The technologies to extract quantitative measures of bone quality for assessment of fracture risk are emerging, but embryonic. Greater understanding of the material properties of bone, and its interaction with structure, will ultimately improve the assessment of fracture risk and monitoring of patients being treated for metabolic bone disease.

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Mechanical stress-induced AP-1 and Smad signalling for osteoblastic differentiation

Daisuke Inoue, Shinsuke Kido and Toshio Matsumoto
Department of Medicine and Bioregulatory Sciences, The University of Tokushima Graduate School Institute of Health Biosciences, Tokushima, Japan

Mechanical stress (MS) plays a major role in maintaining bone mass and strength. We have identified interleukin (IL)-11, an osteogenic cytokine that enhances bone formation and thereby increases bone mass when over-expressed in transgenic mice, as a molecular target of mechanical stress both in vivo by forced running and in vitro by fluid shear stress (FSS) to osteoblasts. FSS as well as IL-11 suppressed adipogenesis while enhancing osteoblastogenesis from bipotential mesenchymal progenitors, and the effect of FSS was abolished by a neutralizing IL-11antibody, supporting a role for IL-11 in MS-induced bone formation. FSS induction of IL-11 gene transcription was largely dependent on an AP-1 site 70 bp upstream of TATA box, and was preceded by induction of DeltaFosB, a FosB splicing variant that is also able to stimulate bone formation in vivo. DeltaFosB induction by FSS occurred at the transcriptional level through a Ca-ERK-CREB signaling pathway. It appears that a heterodimer of DeltaFosB and constitutively expressed JunD confers FSS-induced IL-11 gene transcription because DeltaFosB and JunD siRNA completely abolished the IL-11 induction. These results are consistent with our previous observation that reduced DNA binding activity of JunD is associated with decreased IL-11 expression in marrow stromal cells from aged mice. We also found a putative Smad-binding element (SBE) 35 bp downstream of the AP-1 site in the IL-11 promoter, which prompted us to examine a crosstalk between BMP-Smad and AP-1 signaling pathways. BMP-2 induced IL-11 gene transcription as expected. Further analysis with immunoprecipitation and DNA precipitation assays revealed that Smad1 indeed binds to the SBE and physically interacts with a DeltaFosB/JunD heterodimer binding to the adjacent AP-1 site. The AP-1/Smad1 interaction occurred through the C-terminus of JunD, because C-terminally truncated JunD formed a heterodimer with DeltaFosB on the AP-1 site but failed to recruit Smad1. Based on these results, we propose that a DeltaFosB/JunD/Smad1 complex, on which BMP-2 and AP-1 signaling pathways converge, plays a critical role in MS-induced bone formation.