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

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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.