HOW OSTEOPLAST REGULATES ENERGY METABOLISM AND SYSTEMIC INFLAMMATION DEPENDENT OF FRA-2 EXPRESSION

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Background and Objectives The transcription factor Fra-2 (Fosl2) is a member of the AP-1 complex and an important regulator of bone homeostasis. We have previously shown that Fra-2 controls bone development, osteoclast size [1] and osteoblast differentiation through direct regulation of Collagen IA2 and Osteocalcin (Ocn) [2]. Recent studies have established that the skeleton functions as an endocrine organ affecting metabolism through Ocn [3], although only few transcription factors and only one osteoblast-derived hormone are known to affect the crosstalk between bone and metabolism.

Materials and Methods We have generated mice with specific deletion of Fra-2 (Fosl2) or ectopic expression of Fra-2 in osteoblast to study the role of Fra-2 beyond the bone e.g. in metabolism.

Results Here we show that mice with osteoblast specific deletion of Fra-2 (Fosl2) have despite a low bone mass, an increased body weight. In contrast, ectopic expression of Fra-2 in osteoblasts display increased bone mass and decreased body weight accompanied with reduced serum glucose and insulin levels, improved glucose tolerance and insulin sensitivity. In addition, these Fra-2 mutant mice are protected from metabolic impairment, when challenged with high fat diet (HFD). Surprisingly a systemic inflammation and macrophage infiltration in liver, spleen and lung was observed in Fra-2 osteoblast specific mice. Mechanistically, we showed that in osteoblasts Fra-2 transcriptionally represses an important adipocytokine Adiponectin (Adipoq), while it induces Ocn, both responsible for the glucose and insulin metabolism alteration. Whereas, the systemic inflammation was likely due to the transcriptional increased of Osteopontin (OPN) expression by Fra-2, which is known as a potent inductor of macrophage activation.

Conclusions Taking together these results show that Fra-2 expression in osteoblast transcriptionally modulates Adipoq, Ocn and OPN expression and secretion representing a novel mechanism for the endocrine function of the skeleton on systemic metabolism and inflammation.

References

BASELINE ELEVATED SERUM LEVELS OF CALPROTECTIN AS INDEPENDENT MARKER FOR RADIOPHAGIC SPINAL PROGRESSION IN ANKYLOSING SPONDYLITIS

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Background and Objective Syndesmophytes formation and complete fusion of the total spine are common characteristics leading to functional impairment and disability in ankylosing spondylitis (AS) patients. Predictors for progression of structural damage are smoking, elevated levels of acute phase reactants and the presence of syndesmophytes at baseline. These predictors identify increased risk for progression at group level but their specificity is not strong enough to be used as biomarkers in individual patients. We recently...