Abstract

Genetic analyses have proven the key roles played by the various members of the heterodimeric transcription factor AP-1 in bone homeostasis. More specifically, it was shown that transgenic (tg) mice over-expressing c-Fos developed osteochondrosarcomas caused by transformation of the mesenchymal osteoprogenitor cells. Mice over-expressing Fos family member Fra-1 developed osteosclerosis, a bone phenotype characterised by increased bone formation by the osteoblasts.

The role of Jun family members, which are required to form functional AP-1 transcription factor, in bone development is less known. By analysing *junD*$^{-/-}$ mice, I could identify JunD as a novel player in bone maintenance which negatively regulates bone mass in the aging process.

The analysis of c-Jun in bone development was hampered by inefficient deletion of conditional *c-jun* mice. Nevertheless by means of viral Cre infection of tumor cells derived from *c-fos* tg/*c-jun*$^{fl/fl}$ double mutant mice, I could show that c-Jun is crucial for proliferation and survival of these cells.

To determine the role of JunD in c-Fos induced osteosarma and Fra-1 induced osteosclerosis, I generated double mutants by crossing *junD*$^{-/-}$ mice with *c-fos* tg and *fra-1* tg mice respectively. *fra-1* tg/*junD*$^{-/-}$ double mutants died *in utero* or shortly after birth and could therefore not be analysed. However analysis of *c-fos* tg/*junD*$^{-/-}$ mice revealed a drastic decrease in tumor size. Further investigation demonstrated that tumor initiation was not affected by the lack of JunD but tumor progression was dependant on JunD *in vivo* and *in vitro.* Moreover JunD lacking tumors displayed an increased number of the bone resorbing cells (osteoclasts). Therefore, in addition to modulate tumorigenic properties, JunD also affects tumor size by altering the bone remodeling of the tumors.

In summary this work established JunD as a novel player in bone homeostasis. Moreover this work revealed essential and unexpected functions for JunD in c-Fos induced osteosarcoma.