



## Gfi1: a new therapeutic target for multiple myeloma bone disease

N°218 - January 2012

Inhibition of osteoblast differentiation characterizes multiple myeloma (MM) bone disease and persists even when patients are in long-term remission. The authors of this study [1] developed a murine multiple myeloma model in which the bone marrow stromal cells remained unresponsive to osteoblast differentiation, inhibiting signals after removal of MM cells.

They found that bone marrow stromal cells, in MM-bearing mice and in MM patients, had an increased expression of the transcriptional repressor Gfi1. This factor repressed the transcription factor Runx2 which is critical for osteoblast differentiation. Increased Gfi1 level and Runx2 repression were blocked by anti-TNF- $\alpha$  and IL-7 antibodies. These cytokines are produced massively by MM cells. Importantly, bone marrow stromal cells isolated from Gfi1-/- mice were resistant to MM-induced osteoblastogenesis suppression. Furthermore, Gfi1 knockdown by specific siRNA in bone marrow stromal cells from MM patients restored Runx2 level and osteoblastogenesis markers.

These data highlight the important role of Gfi1 cellular amount in prolonged MM-induced osteoblast suppression and identifies Gfi1 as a new potential therapeutic target for MM bone disease.

1. D'Souza S et al. *Blood*. 2011; doi:10.1182/blood-2011-04-346775.

### Gfi1: a new therapeutic target for multiple myeloma bone disease

In multiple myeloma, osteoblast differentiation is repressed. Lack of osteoblast differentiation leads to generalization of multiple bone lytic lesions. At the cellular level, multiple myeloma cells produce large amounts of interleukin-7 (IL-7) and tumor necrosis factor (TNF- $\alpha$ ). These cytokines induce nuclear localization of growth factor independence-1(Gfi1) in bone marrow stromal cells, including preosteoblast cells. In response to IL-7 and TNF- $\alpha$ , bone marrow stromal cells produce large amounts of Gfi1 protein. In the nucleus, Gfi1 directly binds to Runx2 gene promotor, repressing its transcription. Runx2 is known to promote osteoblastogenesis. Its low cellular concentration affects osteoblast differentiation.

