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第 329 回松本歯科大学大学院セミナー

日　時: 2015 年 7 月 21 日(火)　17 時 30 分～18 時 15 分

場　所: 実習館 2 階 総合歯科医学研究所セミナールーム

演　者: Garson David Roodman 氏(インディアナ大学・教授)

タイトル: Mechanisms of osteoblast suppression in myeloma.

(多発性骨髄腫における骨芽細胞の抑制メカニズム)

Multiple myeloma (MM) is the most frequent cancer to involve the skeleton with 80-90% of patients developing bone lesions. MM bone lesions are purely osteolytic and can cause severe and debilitating bone pain, pathologic fractures, hypercalcemia, spinal cord compression, and increased mortality. MM bone disease is marked by severe dysfunction of both bone formation and resorption with osteoblast activity severely decreased or absent. Further, bone lesions in patients with MM rarely heal, even when the patients are in prolonged complete remission. Multiple factors have been identified that drive osteoclastic bone resorption in MM, but the basis for the severe suppression of bone formation that persists even in the absence of MM cells is less well understood. A number of osteoblast inhibitors produced by MM cells or cells in the MM marrow microenvironment in response to MM cells have been identified, including TNF-α, MIP-1α, and IL-3/Activin A, DKK1, sclerostin, TGFß, hepatocyte growth factor and IL-7. However, these factors do not explain the long term suppression of osteoblast differentiation in MM. We reported that MM cells and primary marrow stromal cells from MM patients express elevated levels of the transcriptional repressor, Gf1; that MM cells induce expression of Gfi1 in marrow stromal cells and that Gfi1 represses *RUNX2* transcription. We recently demonstrated that Gfi1 directly binds *RUNX2* and induces recruitment of chromatin co-repressors that alter the epigenetic state of the *Runx2* gene resulting in prolonged OB suppression. Gfi1 recruits histone modifiers HDAC1, Co-REST, LSD1, and G9a to the *Runx2* gene and reduces the transcriptionally permissive euchromatin marks H3K4me3, H3K9ac, H3K12ac, H3K27ac, and H3K36me3 on *Runx2* . These changes persist even after removal of MM cells and make *Runx2* transcription refractory to OB differentiation signals. Importantly, Gfi1 knockdown in MC4 cells prevented sustained repression of *Runx2.*

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Additionally, we found that Ajuba, a LIM domain containing protein, is required for Gfi1's repression of *Runx2*. Ajuba by itself does not bind or repress *Runx2,* but directly interacts with Gfi1, via its LIM domain, to allow the complex to enter the nucleus and bind *RUNX2*. Knockdown of Ajuba in MC4 cells abolishes Gfi1 repression of *Runx2*. These results suggest that our increased understanding of the pathogenesis of MM bone disease should allow identification of novel therapeutic targets to block or reverse the loss of skeletal integrity MM patients.

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