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Mature Osteoblasts Induce Myeloma Cell Death through Inhibiting the Sp1-TAK1-Pim-2 Pro-survival Pathway

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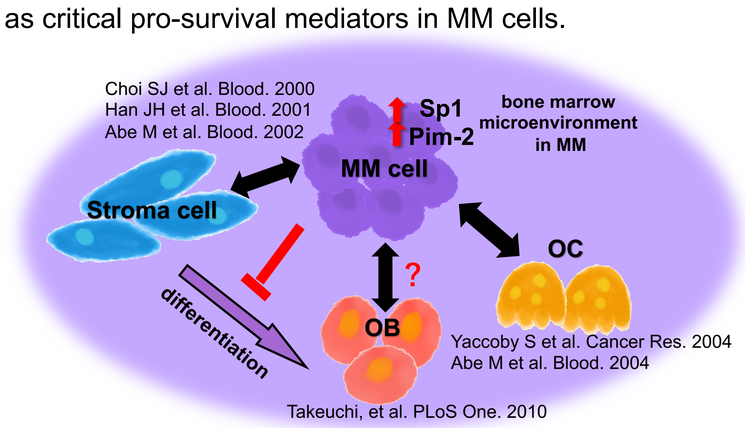
INTRODUCTION

Bone marrow stromal cells (BMSCs) are a major type of cells to support myeloma (MM) cell growth. In sharp contrast to BMSCs, however, we found that mature osteoblasts (OBs) with bone formation were found to induce apoptosis in MM cells (PLoS One 2010). We also reported that Sp1 (Oncotarget 2016) and Pim-2 (Leukemia 2011, 2015) are over-expressed as critical pro-survival mediators in MM cells.



AIM

The suppressive activity for MM cell growth emerged in parallel with the formation of mineralized nodules by OBs and correlated well with the levels of mineralization, although OBs at an early differentiation stage with increased alkaline activity without mineralized nodule formation was not able to reduce the viability of MM cells[1].

However, precise mechanisms for induction of apoptosis in MM cells as well as the intracellular signaling responsible for MM cell death by mature OBs remain largely unknown.

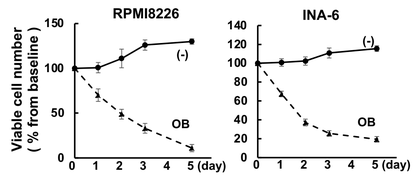
In the present study, we aimed to explore the mechanisms of MM cell growth inhibition by mature OBs differentiated from BMSCs.

METHOD

MC3T3-E1 preosteoblastic cells were differentiated into OBs forming mineralized nodules with rBMP2 in osteogenic media, and used as mature OBs.
MM cell lines were cocultured with mature OBs, and viable cell number and activation of various signaling pathways in MM cells were analyzed.

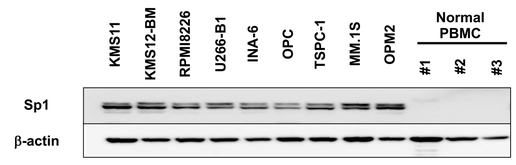
RESULTS

OBs induce MM cell death over time



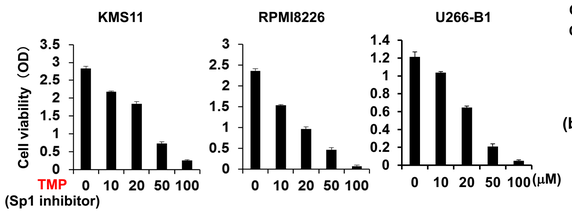
In cocultures with mature OBs, the viability of RPMI8226 and INA-6 MM cells was reduced over time, as we previously reported using several MM cell lines and primary MM cells (Takeuchi, et al 2010).

Sp1 is overexpressed in MM cells

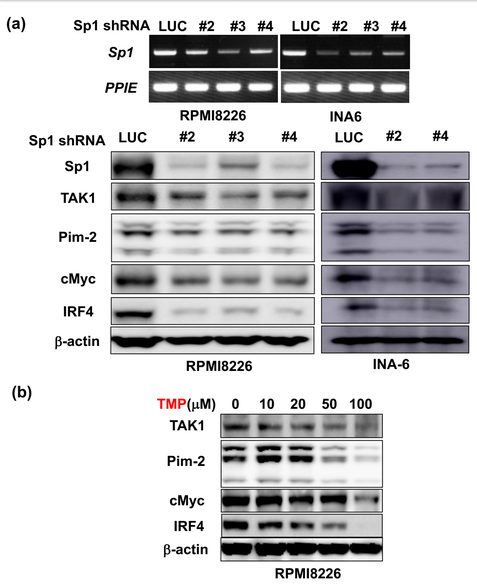


PBMC: peripheral blood mononuclear cell

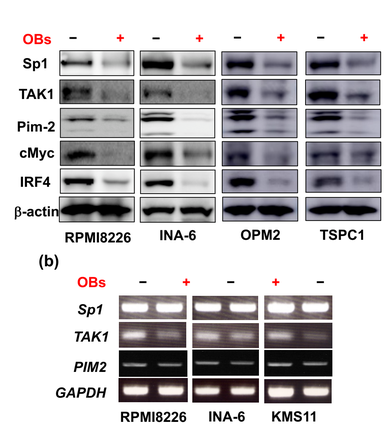
Sp1 is responsible for MM cell growth and survival



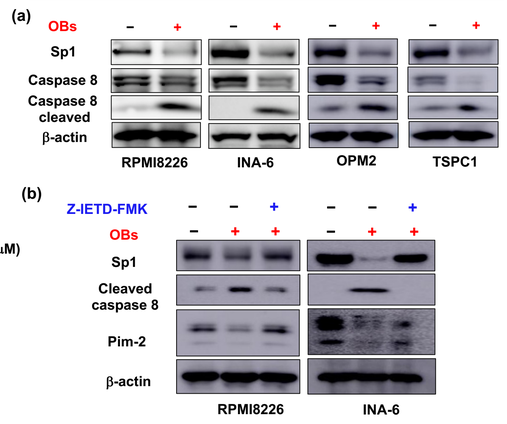
Sp1 inhibition suppresses the critical pro-survival factors for MM cells



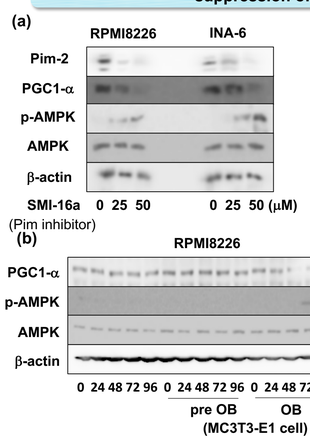
Mature OBs reduce Sp1 at protein but not at mRNA levels



OBs activate caspase 8 to degrade Sp1 in MM cells

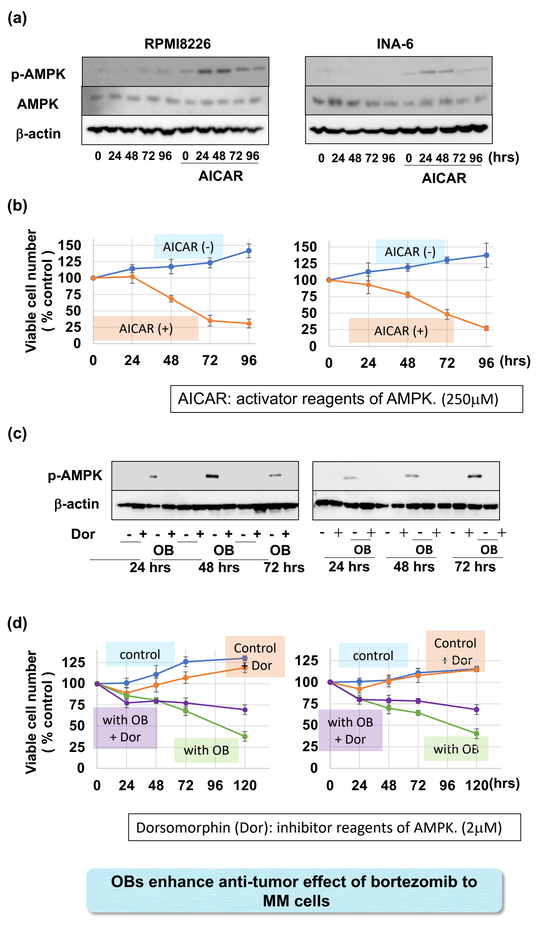


OBs induce the phosphorylation of AMPK in MM cell lines by the suppression of Pim-2 expression



The PGC1-α expression was decreased by addition of SMI-16a, Pim inhibitor, dose dependently in MM cells. (a) Coculture with OBs also decreased the PGC1-α expression in MM cells. (b)

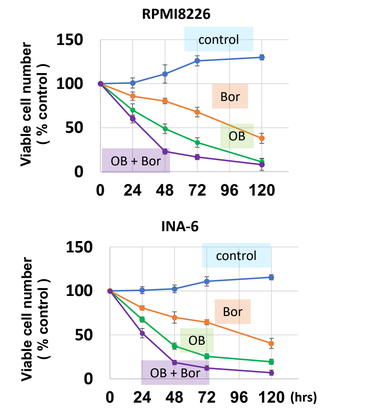
The phosphorylation of AMPK derived by osteoblasts induces apoptosis with cell cycle arrest in MM cells



AICAR: activator reagents of AMPK. (250μM)

Dorsomorphin (Dor): inhibitor reagents of AMPK. (2μM)

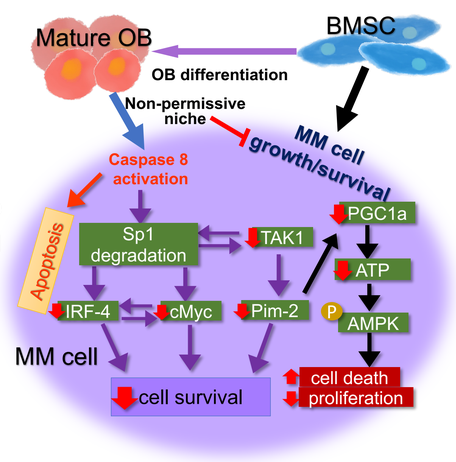
OBs enhance anti-tumor effect of bortezomib to MM cells



MM cell lines, RPMI8226 and INA-6 cells, were cocultured with OBs, with or without bortezomib (Bor) at 5nM. Coculture with OBs enhances anti-tumor effect of bortezomib to MM cells.

CONCLUSIONS

In contrast to MM growth enhancement with activation of the TAK1-Pim-2 pathway by BMSCs and osteoclasts, OBs with mineralized nodule formation are able to induce apoptosis along with inhibition of the Sp1-TAK1-Pim-2-mediated prosurvival pathways and thereby impairing PGC-1α-driven energy production and metabolism.



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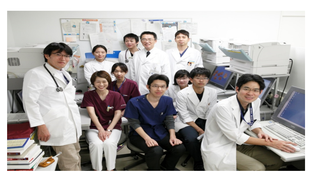

COI Disclosure
No conflicts of interest to declare

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1. Takeuchi K, Abe M, Hiasa M, Oda A, Amou H, Kido S, *et al.* Tgf-Beta inhibition restores terminal osteoblast differentiation to suppress myeloma growth. *PloS one* 2010 Mar 25; **5**(3)**:** e9870.

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