RET Protooncogene Promotes Osteoblastic Bone Metastases

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Background

- Bone metastases are common in MTC; the lesions can be osteolytic, osteoblastic, or mixed.
- RET is a driver oncogene in medullary thyroid carcinoma (MTC), encoding the transmembrane tyrosine kinase receptor. RET mutations cause constitutive activation of the receptor.
- The most frequent RET mutations are at codons W634R and M918T.

Gap of knowledge

The role of RET mutations in the development of bone metastases and associated types of bone lesions is unknown

Hypothesis

There is an association of bone metastases phenotype in MTC and the type of RET mutation

Methods

- MZCRC1 and TT cell lines. TT cells carry a mutation in exon 11 at codon 634 (W634R), and MZCRC1 cells have a mutation in exon 16 at codon 918 (M918T).
- Cultured TT, MZCRC1, and MZCRC1-RET-shRNA were injected into the femurs of SCID male mice.
- MicroCT, radiology and Histomorphometry analysis (BIOQUANT OSTEO software)
- Immunohistochemistry (Ki67)
- Histology (H&E)
- Trap Staining
- Coculture Studies MC3T3-E1 preosteoblast/ conditioned media MTC cells
- Alkaline Phosphatase staining
- Real Time qPCR analysis of bone markers (ALP, RUNX2)

Increase in BMD, trabecular bone volume in TT injected mice

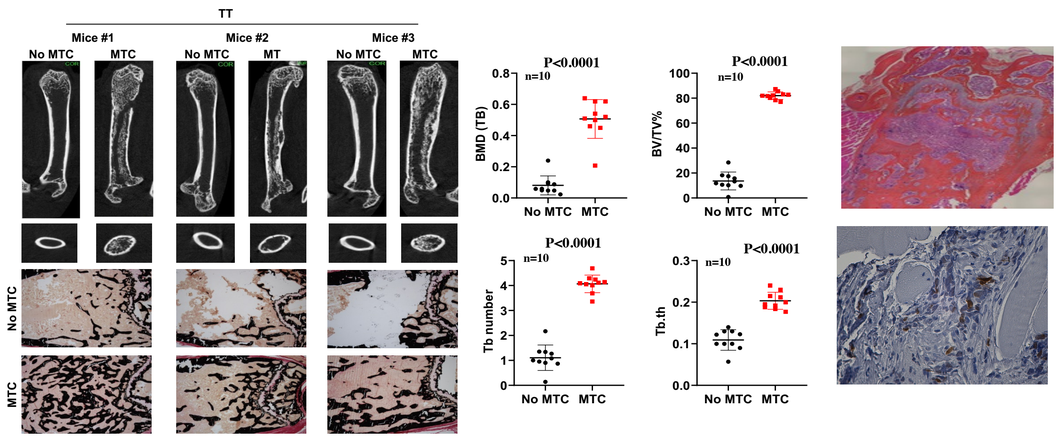

Figure 1. MicroCT and Histology Analysis of TT injected mice

Increase in cortical thickness and porosity in MZCRC1 injected mice is reduced by RET-shRNA

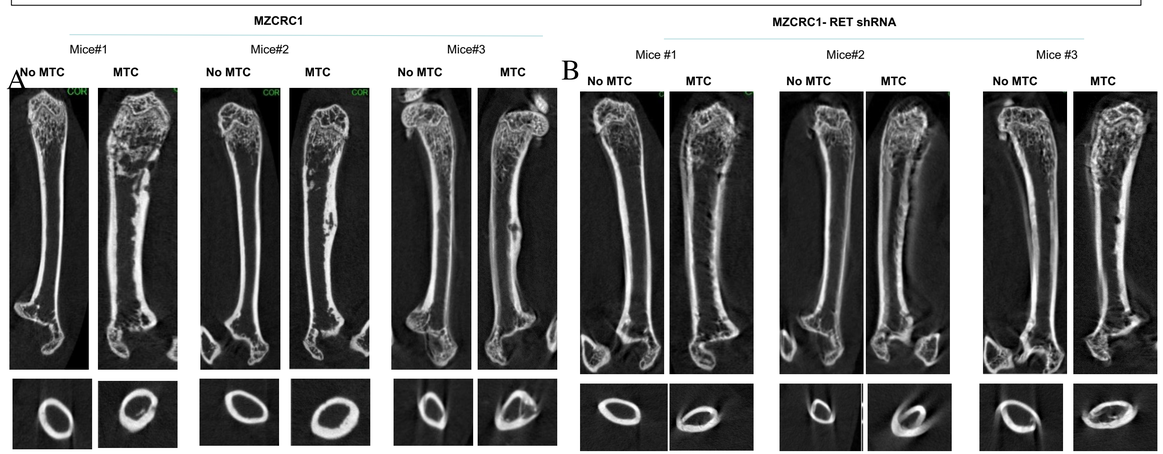

Figure 2. MicroCT Analysis of MZCRC1 and RET-shRNA MZCRC1 injected mice

Conditioned media of MTC cells promotes osteoblast differentiation

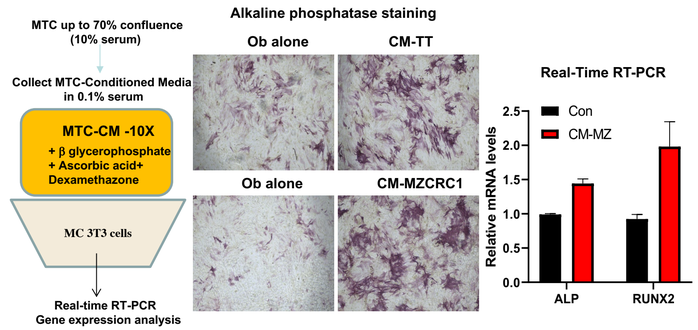

Figure 3. MC3T3-E1 preosteoblast cultured with CM-TT and CM-MZCRC1

Conclusion

- Intrafemoral inoculation of TT and MZCRC1 cells in mice resulted in osteoblastic lesions
- TT cells were associated with increased trabecular bone.
- MZCRC1 was associated with increased cortical thickness and porosity.
- Conditioned media of MZCRC1 and TT cells was associated with osteoblast differentiation and expression of osteogenic markers (ALP, RUNX2).
- Different RET mutations may cause different bone phenotypes via different mechanism

References

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