Regulation of cancer induced osteoclastogenesis by exogenous and tumour-derived Sema3A
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Introduction
Osteolytic bone disease is a common cause of morbidity and significant tumour burden in advanced breast, prostate and osteosarcoma cancer patients. Radiographic lesions observed in cancer patients are osteolytic, resulting from a variety of factors released by primary bone or invading tumour cells that reduce osteoclast activity and cause excessive bone resorption1-3. Semaphorin 3A (Sema3A) was originally identified by its role in axon growth cone guidance but has also been shown to be of importance in bone turnover4,5. Sema3A enhances osteoblast differentiation and inhibits osteoclastogenesis. Furthermore, Sema3A was found to protect against bone loss in mouse models of postmenopausal osteoporosis6. Sema3A also modulates tumour growth and depending on tumour type can be classified as both a tumour suppressor as well as a tumour promoter7,8. In breast cancer, Sema3A reduces migration in vitro and breast cancer growth in vivo9,10. In this study, we hypothesized that Sema3A reduces the motility of cancer cells and inhibits the ability of “bone-tropic” cells to enhance osteoclastogenesis and to cause osteolysis.

Aims
The main aim of this study was to examine the effects of exogenous and tumour-derived Sema3A on:
- bone-tropic cell growth.
- bone-tropic cell motility.
- bone-tropic cell induced osteoclast formation and activity.
- bone-tropic cell induced osteolysis.

Exogenous Sema3A inhibits RANKL and cancer cell induced osteoclast formation

Exogenous and tumour-derived Sema3A regulate cancer cell migration

Stable knockdown of tumour-derived Sema3A enhances osteoclast formation

Exogenous Sema3A has no effects on bone-tropic cancer cell growth

Summary
- Exogenous and tumour-derived Sema3A:
  - inhibits RANKL-stimulated osteoclast formation in vitro.
  - suppresses bone-tropic cell induced osteoclastogenesis.
  - reduces breast cancer cell motility.
  - has no effects on bone-tropic cancer cell growth.
- This identifies Sema3A, or novel peptides that mimics its action, as promising therapeutic agents for the treatment of cancer associated bone disease.
- In vivo studies to test the effects of Sema3A on mouse models of osteolysis are currently in progress.

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References