A SYSTEMS BIOLOGY MODEL TO DESCRIBE LONG-TERM BONE REMODELING EFFECTS OF ESTROGEN IN MENOPAUSAL AND POSTMENOPAUSAL WOMEN

M. M. Riggs, M. C. Peterson, M. R. Gastonguay; Metrum Institute, Tariffville, CT

ABSTRACT

Estrogen has long been proposed to control bone remodeling through multiple cellular mechanisms, including membrane bound osteoclasts and parathyroid hormone. Extracellular fluid calcium (Ca) is sensed by the parathyroid gland through parathyroid hormone (PTH) receptors which couple to calcium, aquaporins, and intracellular signaling pathways. Such signaling results in increased osteoclastogenesis and bone resorption. Estrogen has also been shown to inhibit osteoclast formation and reduce bone remodeling through its anti-osteoclastic effects. More recently, estrogen has been shown to upregulate RANKL expression and enhance TGF-β effects. A multi-factorial system biology approach was used to model estrogen effects on bone remodeling. This model integrates literature data from previously developed systems biology models and emphasizes estrogen effects on RANKL and TGF-β pathways in bone remodeling.

BACKGROUND

- Calcium (Ca) homeostasis and bone remodeling are both physiological requirements
- Involves intracellular signaling, endocrine feedbacks and multiple organs
- Maintains tight control of extracellular fluid (ECF) Ca concentration
- Regulates bone remodeling; maintain bone structure / strength
- Estrogen effects on bone remodeling reported to be mediated through effects on RANKL and TGF-β and transforming growth factor beta (TGFβ)
- A previously developed Ca homeostasis and bone remodeling systems biology model (Figure 1) provided a general platform to evaluate these plausible controlling mechanisms of estrogen on bone remodeling
- Literature reports were reviewed to determine the typical magnitude and time-course of estrogen effects on the following bone remodeling markers:
  - Bone resorption markers (osteoclast function): Urine N-telopeptide (uNTx), Serum C-telopeptide (sCTx)
  - Bone formation marker (osteoblast function): Bone specific alkaline phosphatase (BSAP)
- Literature data digitized: Plot Digitizer 2.41
- Graphics and data management: R version 2.7.2
- Model fitting and simulation: Berkeley Madonana 8.0
- Models components evaluated: (I) inhibit, (II) stimulate
- Direct effects of estrogen on production of TGFβ or RANKL
- Effect of estrogen-TGFβ interaction on osteoblast survival
- Goodness-of-fit diagnostics
  - Graphical
  - Akaike Information Criterion (AIC)

METHODS

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RESULTS

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REFERENCES