Bringing Attention to Lesser-known Bone Remodeling Pathways

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Abstract

Context: Osteoporosis, a disease of low bone mass, places individuals at enhanced risk for fracture, disability, and death. By 2025, the number of fractures due to osteoporosis is expected to rise to nearly three million in the USA alone. Pharmacological treatments for osteoporosis are aimed at stabilizing or increasing bone mass. However, there are significant drawbacks to current pharmacological options, particularly for long-term management of this chronic condition. Moreover, the drug development pipeline is relatively bereft of new strategies. Consequently, there is an urgent and unmet need for developing new strategies and targets for treating osteoporosis.

Objective: Casual observation led us to hypothesize that much of the bone remodeling research literature focused on relatively few molecular pathways. This led us to perform bibliometric analyses to determine the relative popularity of bone remodeling pathways in publications and US National Institutes of Health funding of the last 10 years. In this review article, we discuss these findings and highlight several less-examined signaling pathways.

Methods

- A literature search was performed in PubMed.gov using keywords specific to bone remodeling with results from January 1, 2008 to December 31, 2017.
- We then combined terms relating to the same signaling pathway to identify popular pathways in the field.
- To more narrowly examine the skeletal literature, we included the search term ‘osteoblast’ or ‘osteocyte’ or ‘osteoclast’.
- In order to identify lesser-studied pathways in bone remodeling, we excluded pathways with 50 or greater publications in the last 10 years.
- to identify particularly notable pathways for the focus of this review article, we generated the following inclusion criteria: (1) functional evidence published in a peer-reviewed journal and indexed in PubMed.gov, (2) fewer than ten review articles published about the pathway in the skeleton in the last 10 years, and (3) identifiable as a distinct signaling pathway.

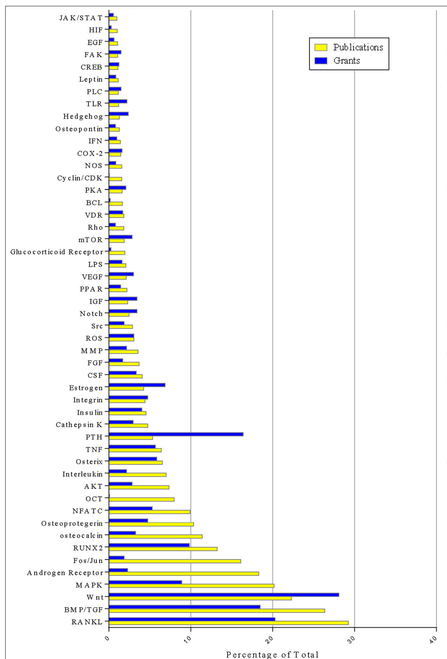

Fig. 1 Fifty most popular pathways in publications and funded grants (indexed in PubMed.gov and NIH Reporter, respectively) from January 1, 2008, to December 31, 2017, as identified using the search terms detailed in Supplemental Table 2 in combination with the search Bskeleton or Bbone and Bsignaling or Bpathway and Bosteoblast or Bosteocyte or Bosteoclast.

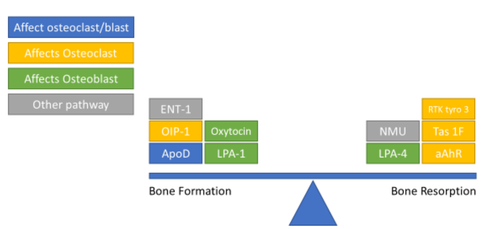

Fig. 2 Summary of the overall effect of the lesser known pathways on bone formation and resorption that were found in this study.

Results

Apolipoprotein D: Global ApoD KO mice exhibit low bone mass in both trabecular and cortical compartments of the femur that is associated with increased bone turnover rate. ApoD knockout mice display an increased ratio of Rankl:Opg and increased osteoclast number and decreased osteoblast differentiation.

Aryl Hydrocarbon receptor: When active, AhR modulates gene expression and induces osteoclastogensis by increasing the expression of estrogen metabolizing and synthesizing enzymes, such as Cyp1b1 and aromatase and IL-1B, IL-6. AhR’s bone remodeling effect was only significant when its activity was affected in osteoclast, not osteoblast.

Lysophosphatidic Acid: LPA signaling via LPA receptor 1 (LPA1) promotes osteoblastogenesis while LPA signaling via LPA receptor 4 (LPA4) restricts osteoblastogenesis.

Osteoclast inhibitory peptide-1: OIP-1 binds the Fc gamma receptor IIB to inhibit osteoclast differentiation. OIP-1 Tg mice exhibit decreased osteoclast progenitors and suppression of TRAF-2, c-Fos, p-c-Jun, and NFATc1 protein levels after RANKL stimulation; Spleen tyrosine kinase activation is also inhibited.

Oxytocin: oxytocin promotes osteoblastic differentiation of osteogenic cells in vitro. OTR is expressed in osteoblasts and its specific deletion in these cells leads to low bone mass.

Tas 1 Family: Consistent with a role in osteoclast function, Tas1R3 and its putative partner Tas1R2 are expressed in primary osteoclasts and high bone mass in Tas1R3 knockout mice is associated with decreased serum levels of the bone resorption marker.

NMU: global homozygous knockout of NMU leads to high trabecular bone mass in femora due to increased bone formation rate.

RTK: Tyro3 activation promotes osteoclast activity in vitro; global homozygous deletion of which leads to high bone mass in tibiae of 10-week-old mice.

ENT-1: Is involved in uptake of Adenosine; its global knockout leads to low bone mass in the vertebrae of 7-month-old mice and is associated with increased osteoclast number.

Conclusion

- our bibliometric analysis indicates a striking lack of heterogeneity within the bone remodeling field—with just three pathways accounting for more than 50% of publications and nearly 50% of funded NIH grants in this field during the last 10 years.
- We are concerned that this current lack of diversity may restrict discovery of novel therapeutic.
- Here, we present brief overviews of several pathways for which functional evidence (genetic, pharmacological, etc.) indicates a role in the regulation of osteoblasts and/or osteoclasts. Additional work is required to elucidate the mechanism(s).