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Extracellular Vesicles and Circulating Nucleic Acids

Commentary

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Gas-powered extracellular vesicles promote bone regeneration

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Abstract

The signaling gas hydrogen sulfide (H_2S) has recently been implicated in the regulation of bone remodeling and the maintenance of periodontal health. Exploring the underlying mechanisms for this regulation holds promise for the development of new treatment strategies to block bone resorption and stimulate bone regeneration. A recent study by Zhou *et al.* (Bioactive Materials, 2024) showed that treatment with H_2S stimulated changes in the extracellular vesicles (EVs) released by M2 macrophages, enhancing their capacity to promote the osteogenic differentiation of mesenchymal stem cells *in vitro.* The H_2S-stimulated EVs, given together with mesenchymal stem cells (MSCs), also promoted bone regeneration *in vivo* in a mouse calvarial critical-size defect model. This activity was linked to augmented expression of moesin, a membrane-cytoskeletal linkage protein, which was found at increased levels in EVs from cells stimulated by H_2S. The study identifies a new strategy for generating EVs that are pro-osteogenic. It also uncovers a surprising role for moesin in stimulating osteogenesis in MSCs.

Keywords: Osteogenesis, exosomes, hydrogen sulfide, moesin, Wnt/β-catenin, macrophage, osteoblast

COMMENTARY

Until 1996, hydrogen sulfide (H_2S) was considered a toxic gas. However, that perception changed when Abe and Kimura showed that H_2S, along with its producing enzyme cystathionine β-synthase, is highly expressed

in the hippocampus. They found that H_2S produced by cystathionine β-synthase selectively enhances N-methyl-D-aspartate (NMDA) receptor-mediated responses and facilitates the induction of hippocampal long-term potentiation[1]. Subsequent studies identified cystathionine γ-lyase and 3-mercaptopyruvate sulfurtransferase as additional H_2S-generating enzymes in mammalian cells, thereby completing the enzymatic system responsible for H_2S production[2]. This discovery positioned H_2S alongside nitric oxide (NO) and carbon monoxide (CO) as a signaling gas[3]. H_2S has since been shown to mediate vasodilation[4], exhibit anti-tumor and anti-metastatic properties, and regulate bone remodeling[3,5,6]. In addition to its role in enhancing NMDA receptor-mediated responses, several mechanisms have been suggested to account for the signaling effects of H_2S, including the activation of ATP-sensitive potassium channels[7,8], the stimulation of endothelial nitric oxide synthase (eNOS) to increase NO production[9], and the inhibition of voltage-gated calcium channels[10]. By inducing S-sulfhydration of a ubiquitin-ligase, H_2S was shown to regulate CD36 vesicle transport in diabetic hearts[11]. H_2S has been reported to have either pro-inflammatory or anti-inflammatory effects[12,13]. It has been implicated in regulating macrophages during inflammatory stimulation[14]. Additionally, it was recently shown to be involved in anti-viral responses, including the response to SARS-CoV-2[15]. Because of its potential therapeutic activities, small molecule H_2S donors have been developed and are being tested as therapeutic tools[6].

This commentary is focused on a recent study by Zhou *et al.* that described a novel mechanism by which H_2S regulates bone regeneration[16] [Figure 1]. It was reported that a slow-release donor of H_2S, GYY4137, stimulated the polarization of M2 macrophages and changes in the composition of extracellular vesicles (EVs) released from these cells. In the manuscript, the authors referred to the extracellular vesicles as exosomes. However, based on the data they presented and by the International Society of EVs recommendations[17], I will refer to these vesicles as EVs throughout this commentary. H_2S-stimulated EVs from M2 macrophages, together with mesenchymal stem cells (MSCs), increased bone formation when used in a scaffold to fill critical size defects in mouse calvaria. Liquid Chromatography/Mass spectroscopy was employed to examine the protein composition of EVs from M2 macrophages with or without H_2S treatment. From this analysis, the membrane-cytoskeleton linkage protein moesin was identified as a candidate for mediating the increased osteogenic effects. RNA interference knockdown of moesin in M2 macrophage resulted in EVs that were less able to exert osteogenic effects on MSCs. Surprisingly, recombinant moesin added to MSCs increased osteogenic differentiation. Taken together, these data suggest that pre-treating M2 macrophages with H_2S induces them to secrete EVs that have therapeutic potential for use in situations where bone regeneration is required. Moesin is a component of the mechanism of action leading to this regulatory activity.

Previous studies have shown that M2 macrophages produce paracrine factors that promote osteogenesis[18-20]. Of these paracrine factors, several groups reported that EVs were key contributors[21-26]. In the current study, it was reported that H_2S conditioned media from M2 macrophages stimulated osteogenic differentiation of MSCs. Evidence included increased expression of alkaline phosphatase and runt-related transcription factor 2 (*RUNX2*) genes, increased alkaline phosphatase enzymatic activity, and more deposition of mineral crystals *in vitro*. These experiments confirmed previous reports and provided a solid experimental platform for further experimentation.

Having found that conditioned media from M2 macrophages promotes osteogenesis, Zhou *et al.* then tested whether pre-treatment of the macrophages with H_2S would affect the regulatory activity of the conditioned media[16]. Their data showed the conditioned media from H_2S-stimulated M2 macrophages displayed a significantly increased ability to promote osteogenic differentiation of MSCs.

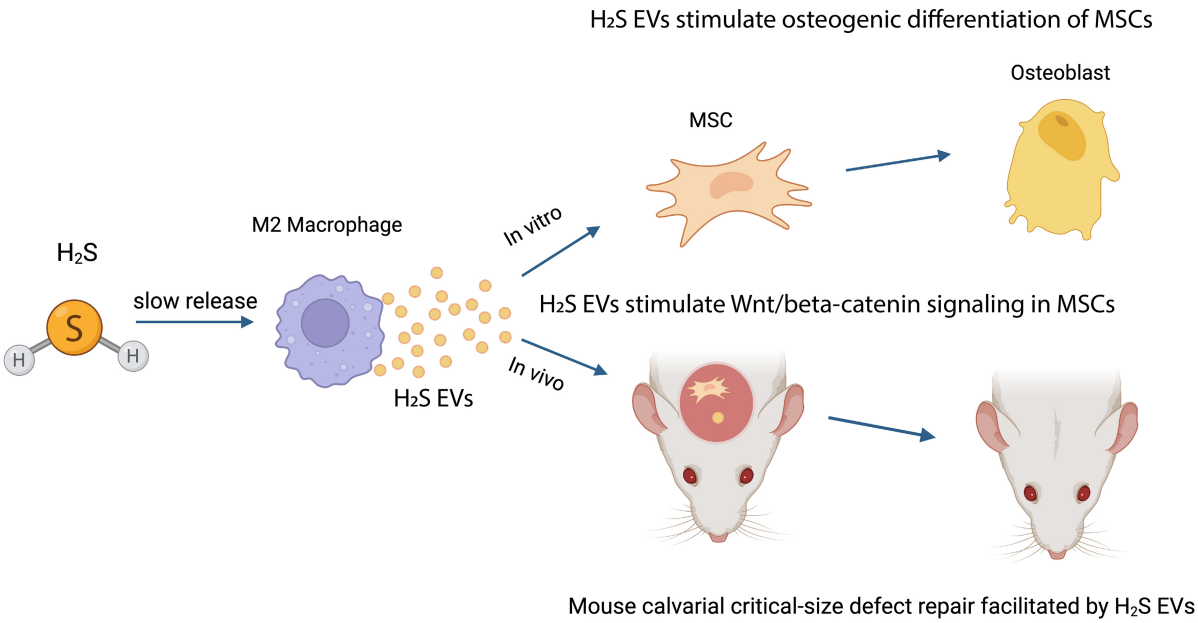

Figure 1. Schematic of findings of Zhou *et al.*[16]. H_2S-stimulated M2 macrophages produce EVs that have increased ability to promote differentiation of MSCs into osteoblasts *in vitro*. When H_2S-stimulated EVs were incorporated into Matrigel along with MSCs, which was then used to fill calvarial critical-size defects in mice, bone regeneration occurred significantly more quickly than when unstimulated M2 macrophage EVs or no EVs were used with MSCs. H_2S: Hydrogen sulfide; EVs: extracellular vesicles; MSCs: mesenchymal stem cells.

EVs were then isolated from the conditioned media by differential centrifugation. It was confirmed that the protocol employed yielded EVs using standard techniques including electron microscopy, nanoparticle tracking, and immunoblots for markers of EVs and of potential contaminants. They found that H_2S stimulation did not significantly change the number of EVs produced. They characterized EVs, comparing EVs from macrophages, M2 macrophages, or H_2S-stimulated M2 macrophages. Among their findings were that EVs for H_2S-stimulated M2 macrophages showed an increased ability to be taken up by target MSCs. This was measured by labeling the EVs with PKH26, a fluorescent membrane vital dye, and then incubating the labeled EVs with MSCs. Although this does not provide quantitative information regarding the absolute efficiency of EV incorporation by the MSCs, it does suggest that EVs from H_2S-stimulated M2 macrophages are taken up more efficiently relative to the EVs from unstimulated cells.

EVs from both M2 macrophages and H_2S-stimulated M2 macrophages promoted osteogenesis in the MSCs *in vitro*, with effects comparable to those induced by conditioned media. The EVs were then tested *in vivo* by mixing them with MSCs in Matrigel, which was used to fill critical-sized defects in mice. The H_2S-stimulated M2 macrophage EVs in Matrigel with MSCs stimulated bone regeneration in the defects better than the same amount of unstimulated M2 macrophage EVs, or Matrigel alone.

To examine the underlying mechanism, differences in the proteins found in the M2 macrophage-derived EVs were compared with the EVs from the macrophages treated with H_2S. This analysis suggested the involvement of the membrane-cytoskeletal linkage protein, moesin, which was found at higher levels in EVs from the H_2S-stimulated M2 macrophage. To test the role of moesin, RNA interference was used to knock down the expression of moesin in the H_2S-treated M2 macrophages. EVs from moesin knockdown cells displayed decreased osteogenic stimulation. Evidence was provided that the EVs were acting by stimulating wingless-related integration site (Wnt)/β-catenin signaling, which promoted osteogenesis. Interestingly, the simple addition of recombinant moesin to the MSCs also increased osteogenesis.

Moesin is a membrane cytoskeletal linkage protein that is often found in filopodia[27]. It is a member of the ezrin-radixin-moesin (ERM) family of linkers[28]. Moesin is thought to be located on the cytoplasmic face of the plasma membrane; in EVs, it would be expected to be in the lumen, and thus not exposed to the surface of the target cell. There are also reports of moesin entering the nucleus, where it is involved in gene expression and mRNA export[29].

Zhou *et al.* hypothesized that moesin in EVs promoted the uptake of EVs by MSCs, which was required for the promotion of osteogenic differentiation[16]. In our view, moesin could act at various levels to promote EV uptake based on its known activities. First, moesin is involved in the regulation of focal adhesions[30]. Changes in this regulation could alter regulatory EVs. We found that EVs from osteoclasts on different substrates have different protein compositions and regulatory activity due to the signals received from the extracellular matrix[31]. This could be consistent with moesin acting at this level. Indeed, we detected moesin at high levels in EVs from osteoclasts on bone or odontoclasts on dentine, but at much lower levels in EVs from osteoclasts on plastic[31]. Second, moesin could be involved in EV formation. Unfortunately, the number of EVs isolated from moesin knockdown cells compared with moesin-replete cells was not reported. Third, moesin could be directly involved in sorting regulatory proteins or other molecules into EVs. A proteomic study of moesin-knockdown EVs would be helpful in testing this idea. Fourth, moesin could facilitate the targeting and uptake of EVs to MSCs. For example, moesin could be a component of a stabilizing complex for a receptor that enables EV uptake. Evidence for EVs containing stabilizing complexes for receptors was discussed in detail in a recent review[32]. Fifth, once incorporated into MSCs, moesin could facilitate the formation of a signaling complex in the MSCs. Along that line, it is intriguing that the prorenin receptor (ATP6AP2), which is found at high levels in EVs from osteoclasts - cells related to macrophages - was implicated as a component of the Wnt/β-catenin signaling complex[33]. Moesin activates Wnt/β-catenin by regulating the phosphorylation state of CD44 and the trafficking of CD44 to the plasma membrane[34,35]. Perhaps when EVs from M2 macrophages fuse with MSCs, they supply multiple components (moesin, prorenin receptor) that stimulate Wnt/β-catenin signaling. Sixth, moesin introduced into the cytosol of target cells after EV fusion could be transported to the nucleus, where it could alter gene expression or mRNA export[29].

As described above, in the report, recombinant moesin added to MSCs increased osteogenic differentiation. This experiment is difficult to reconcile with the hypothesized mechanism and known functions and location of moesin in cells as described above. This finding may point to a new activity of moesin. This conclusion requires significant further verification, but other cytoskeletal proteins, including thymosin beta-4, have roles both inside and outside the cell[36].

Before Zhou *et al.*[16], a recent study had shown that treatment of MSCs with H_2S resulted in variations in the composition of the EVs the cells produced and changes in the EVs' regulatory activity[37]. Currently, a concerted effort by both the pharmaceutical industry and basic scientists is underway to explore ways to enhance or inhibit the production of regulatory EVs. Various agents have also been reported to alter EV composition and regulatory activity. Our group, as described above, reported that the substrate osteoclasts adhere to regulates the overall protein composition of EVs produced by 10%-30%, and importantly, the abundance of the regulatory molecule RANK[31,38]. A high-throughput screen of 4,580 pharmacologically active compounds identified 22 that were potent activators or inhibitors of EV production[39]. Although this seems a small portion, the assay used in this study only detected changes in CD63-containing EVs, which was accomplished by linking CD63 to green fluorescent protein and then screening for fluorescence in EV fractions. The same sort of assay could be used for cells producing specific regulatory molecules (for example, moesin) found in EVs. Based on Zhou *et al.*'s study, H_2S would not be found to generally increase

EV production and would not be detected in the high throughput assay for CD63-containing EVs described above, but instead would alter the regulatory molecules present, including moesin, and would be detected by a screen for moesin levels[16].

In addition to H_2S, NO has been shown to regulate the activity of EVs, increasing the pro-angiogenic effects of EVs from MSCs[40]. Like H_2S and H_2S donors, NO and NO donors have the capacity to modulate regulatory EV production in at least some cell types. Understanding how specific signaling molecules and therapeutic agents affect regulatory EVs is at a very early stage, and Zhou *et al.* represent a significant contribution to this ongoing effort[16].

STRENGTHS, LIMITATIONS, AND FUTURE DIRECTIONS

A primary strength of the study was the multi-level approach, examining the effects of H_2S *in vitro* and *in vivo*. The *in vitro* approach included proteomic assessment, which identified a potential mechanistic element in moesin. In most cases, the experiments were well done, using multiple confirmatory approaches to increase confidence in the result. An important weakness was the quantitation of EVs by protein concentration. During EV isolations, contaminating proteins like albumin from serum are often the major protein component in EV preparations. This makes replication of the experiments described a problem. The finding that recombinant moesin added to MSCs increased osteogenesis is surprising and potentially of great importance because it is very unexpected. Follow-up experiments, such as determining the domain of moesin responsible for the activity, would be exciting. Indeed, showing that soluble moesin is an important intercellular regulatory molecule could be the most generally important finding from the study. Studies examining changes in the number and composition of EVs after moesin knockdown would also be useful. Finally, Zhou *et al.* did not address the signaling pathway through which H_2S triggered changes in EVs[16]. NMDA agonists and antagonists are available and could be used to test whether H_2S affects EV production by NMDA receptors.

Future work that follows Zhou *et al.*'s includes testing whether H_2S has a role in the physiological regeneration of bone[16]. Studies showing a physiologic role of H_2S in orthodontic tooth movement, orthodontic root resorption, and periodontal disease suggest that this may be the case[41-43]. Even if H_2S is not normally involved in bone regeneration under physiological conditions, the current data indicate that stimulation of pro-osteogenic EVs from M2 macrophages may be a useful approach to enhancing bone regeneration. A crucial experiment to understand the underlying mechanism of the EVs is to determine the absolute efficiency of EV fusion with target cells, and whether luminal components of EVs enter the cytosol of the MSCs. The signaling mechanism by which H_2S affects EV production is also vitally important. For example, if H_2S acts through NMDA receptors, then existing NMDA agonists could be used to stimulate the osteogenic EVs[44]. It will be crucial to work out the mechanism by which these EVs and moesin are involved in stimulating the osteogenic differentiation of MSCs in detail. Such work could lead to "next-generation" therapeutic strategies for bone regeneration and other clinical challenges.

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Authors' contributions

Read the source article for the commentary: Holliday LS, Neubert JK, Yang X

Wrote the initial draft: Holliday LS
Made comments, suggestions, and revisions to improve the commentary: Neubert JK, Yang X
Created the initial figure: Holliday LS
Revised the figure: Yang X
Read and approved the final draft: Holliday LS, Neubert JK, Yang X

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Not applicable.

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Conflicts of interest
Holliday LS is an Editorial Board member of the journal *Extracellular Vesicles and Circulating Nucleic Acids*. Holliday LS was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication
Not applicable.

REFERENCES
1. Abe K, Kimura H. The possible role of hydrogen sulfide as an endogenous neuromodulator. *J Neurosci.* 1996;16:1066-71. DOI PubMed PMC
2. Cirino G, Szabo C, Papapetropoulos A. Physiological roles of hydrogen sulfide in mammalian cells, tissues, and organs. *Physiol Rev.* 2023;103:31-276. DOI PubMed
3. Oza PP, Kashfi K. The triple crown: NO, CO, and H_2S in cancer cell biology. *Pharmacol Ther.* 2023;249:108502. DOI PubMed PMC
4. Yang G, Wu L, Jiang B, et al. H2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. *Science.* 2008;322:587-90. DOI PubMed PMC
5. Jiang M, Wang T, Yan X, et al. A novel rhein derivative modulates bone formation and resorption and ameliorates estrogen-dependent bone loss. *J Bone Miner Res.* 2019;34:361-74. DOI PubMed
6. Zhang CH, Jiang ZL, Meng Y, et al. Hydrogen sulfide and its donors: novel antitumor and antimetastatic agents for liver cancer. *Cell Signal.* 2023;106:110628. DOI PubMed
7. Tang G, Wu L, Liang W, Wang R. Direct stimulation of K(ATP) channels by exogenous and endogenous hydrogen sulfide in vascular smooth muscle cells. *Mol Pharmacol.* 2005;68:1757-64. DOI PubMed
8. Yang W, Yang G, Jia X, Wu L, Wang R. Activation of KATP channels by H2S in rat insulin-secreting cells and the underlying mechanisms. *J Physiol.* 2005;569:519-31. DOI PubMed PMC
9. Kida M, Sugiyama T, Yoshimoto T, Ogawa Y. Hydrogen sulfide increases nitric oxide production with calcium-dependent activation of endothelial nitric oxide synthase in endothelial cells. *Eur J Pharm Sci.* 2013;48:211-5. DOI PubMed
10. Makarenko VV, Peng YJ, Yuan G, et al. CaV3.2 T-type Ca^{2+} channels in H_2S-mediated hypoxic response of the carotid body. *Am J Physiol Cell Physiol.* 2015;308:C146-54. DOI PubMed PMC
11. Yu M, Du H, Wang B, et al. Exogenous H_2S induces Hrd1 S-sulfhydration and prevents CD36 translocation via VAMP3 ubiquitylation in diabetic hearts. *Aging Dis.* 2020;11:286-300. DOI PubMed PMC
12. Leslie M. Inflammation's stop signals. *Science.* 2015;347:18-21. DOI PubMed
13. Ye S, Jin N, Liu N, et al. Gases and gas-releasing materials for the treatment of chronic diabetic wounds. *Biomater Sci.* 2024;12:3273-92. DOI PubMed

14. Cao H, Zhou X, Zhang J, et al. Hydrogen sulfide protects against bleomycin-induced pulmonary fibrosis in rats by inhibiting NF-κB expression and regulating Th1/Th2 balance. *Toxicol Lett.* 2014;224:387-94. DOI PubMed
15. Datzmann T, Merz T, McCook O, Szabo C, Radermacher P. H2S as a therapeutic adjuvant against COVID-19: why and how? *Shock.* 2021;56:865-7. DOI PubMed PMC
16. Zhou YK, Han CS, Zhu ZL, et al. M2 exosomes modified by hydrogen sulfide promoted bone regeneration by moesin mediated endocytosis. *Bioact Mater.* 2023;31:192-205. DOI PubMed PMC
17. Welsh JA, Goberdhan DCI, O'Driscoll L, et al; MISEV Consortium. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles.* 2024;13:e12404. DOI PubMed PMC
18. Horibe K, Hara M, Nakamura H. M2-like macrophage infiltration and transforming growth factor-β secretion during socket healing process in mice. *Arch Oral Biol.* 2021;123:105042. DOI PubMed
19. Schlundt C, Fischer H, Bucher CH, Rendenbach C, Duda GN, Schmidt-Bleek K. The multifaceted roles of macrophages in bone regeneration: a story of polarization, activation and time. *Acta Biomater.* 2021;133:46-57. DOI PubMed
20. Kong L, Wang Y, Smith W, Hao D. Macrophages in bone homeostasis. *Curr Stem Cell Res Ther.* 2019;14:474-81. DOI PubMed
21. Zhang C, Bao LR, Yang YT, Wang Z, Li Y. [Role of M2 macrophage exosomes in osteogenic differentiation of mouse bone marrow mesenchymal stem cells under high-glucose and high-insulin]. *Sichuan Da Xue Xue Bao Yi Xue Ban.* 2022;53:63-70. DOI PubMed PMC
22. Liu K, Luo X, Lv ZY, et al. Macrophage-derived exosomes promote bone mesenchymal stem cells towards osteoblastic fate through microRNA-21a-5p. *Front Bioeng Biotechnol.* 2021;9:801432. DOI PubMed PMC
23. Bin-Bin Z, Da-Wa ZX, Chao L, et al. M2 macrophagy-derived exosomal miRNA-26a-5p induces osteogenic differentiation of bone mesenchymal stem cells. *J Orthop Surg Res.* 2022;17:137. DOI PubMed PMC
24. Chen X, Wan Z, Yang L, et al. Exosomes derived from reparative M2-like macrophages prevent bone loss in murine periodontitis models via IL-10 mRNA. *J Nanobiotechnology.* 2022;20:110. DOI PubMed PMC
25. Li Z, Wang Y, Li S, Li Y. Exosomes derived from M2 macrophages facilitate osteogenesis and reduce adipogenesis of BMSCs. *Front Endocrinol.* 2021;12:680328. DOI PubMed PMC
26. Kang M, Huang CC, Lu Y, et al. Bone regeneration is mediated by macrophage extracellular vesicles. *Bone.* 2020;141:115627. DOI PubMed PMC
27. Sauvanet C, Wayt J, Pelaseyed T, Bretscher A. Structure, regulation, and functional diversity of microvilli on the apical domain of epithelial cells. *Annu Rev Cell Dev Biol.* 2015;31:593-621. DOI PubMed
28. Ogihara T, Mizoi K, Kamioka H, Yano K. Physiological roles of ERM proteins and transcriptional regulators in supporting membrane expression of efflux transporters as factors of drug resistance in cancer. *Cancers.* 2020;12:3352. DOI PubMed PMC
29. Bajusz C, Kristó I, Abonyi C, et al. The nuclear activity of the actin-binding Moesin protein is necessary for gene expression in *Drosophila*. *FEBS J.* 2021;288:4812-32. DOI PubMed
30. Frame MC, Patel H, Serrels B, Lietha D, Eck MJ. The FERM domain: organizing the structure and function of FAK. *Nat Rev Mol Cell Biol.* 2010;11:802-14. DOI PubMed
31. Rody WJ Jr, Chamberlain CA, Emory-Carter AK, et al. The proteome of extracellular vesicles released by clastic cells differs based on their substrate. *PLoS One.* 2019;14:e0219602. DOI PubMed PMC
32. Holliday LS, Faria LP, Rody WJ Jr. Actin and actin-associated proteins in extracellular vesicles shed by osteoclasts. *Int J Mol Sci.* 2019;21:158. DOI PubMed PMC
33. Cruciat CM, Ohkawara B, Acebron SP, et al. Requirement of prorenin receptor and vacuolar H+-ATPase-mediated acidification for Wnt signaling. *Science.* 2010;327:459-63. DOI PubMed
34. Martin-Orozco E, Sanchez-Fernandez A, Ortiz-Parra I, Ayala-San Nicolas M. WNT signaling in tumors: the way to evade drugs and immunity. *Front Immunol.* 2019;10:2854. DOI PubMed PMC
35. Orian-Rousseau V. CD44 acts as a signaling platform controlling tumor progression and metastasis. *Front Immunol.* 2015;6:154. DOI PubMed PMC
36. Kleinman HK, Kulik V, Goldstein AL. Thymosin β4 and the anti-fibrotic switch. *Int Immunopharmacol.* 2023;115:109628. DOI PubMed
37. Chu X, Liu D, Li T, et al. Hydrogen sulfide-modified extracellular vesicles from mesenchymal stem cells for treatment of hypoxic-ischemic brain injury. *J Control Release.* 2020;328:13-27. DOI PubMed
38. Holliday LS PS, Rody WJ Jr. RANKL and RANK in extracellular vesicles: surprising new players in bone remodeling. *Extracellular Vesicles Circ Nucl Acids.* 2021;2:18-28. DOI PubMed PMC
39. Datta A, Kim H, McGee L, et al. High-throughput screening identified selective inhibitors of exosome biogenesis and secretion: a drug repurposing strategy for advanced cancer. *Sci Rep.* 2018;8:8161. DOI PubMed PMC
40. Du W, Zhang K, Zhang S, et al. Enhanced proangiogenic potential of mesenchymal stem cell-derived exosomes stimulated by a nitric oxide releasing polymer. *Biomaterials.* 2017;133:70-81. DOI PubMed
41. Lu C, Chen L, Hua Y. Cystathionine gamma lyase aggravates orthodontic root resorption in mice. *Ann Transl Med.* 2019;7:787. DOI PubMed PMC

42. Liu F, Wen F, He D, et al. Force-induced H_2S by PDLSCs modifies osteoclastic activity during tooth movement. *J Dent Res.* 2017;96:694-702. DOI PubMed
43. Song D, He J, Cheng T, et al. Cystathionine γ-lyase contributes to exacerbation of periodontal destruction in experimental periodontitis under hyperglycemia. *J Periodontol.* 2024;Epub ahead of print. DOI PubMed
44. Planells-Cases R, Pérez-Payá E, Messeguer A, Carreño C, Ferrer-Montiel A. Small molecules targeting the NMDA receptor complex as drugs for neuropathic pain. *Mini Rev Med Chem.* 2003;3:749-56. DOI PubMed