Commentary

Gut Microbiome, Bone Health, and Air Pressure: Construing the Axis for the Proposed Triad

Vibhor Joshi[1]

1. G707 Environmental Biotechnology Genetics and Molecular Biology Department, Indian Council of Medical Research, New Delhi, India

Joint pain is common when there is a change in the weather. Mostly, cloudy weather is associated with back pain and knee joint pain. Atmospheric pressure plays a shrouded role in inducing and regulating joint pain. Bones are the densest organs of the human body, and that is why it becomes interesting to see the effect of low-density air pressure on such high-density organs. HIF is one factor involved in air pressure sensing, but how it communicates the signal to bones and the gut will be an interesting mechanism to decipher. The surrounding atmosphere also intervenes in the gut microbiome composition and eventually can change the chemistry of gases produced in the hindgut. IL-8, IL-6, and TLR-4 are a few of the signal-carrying molecules for the hindgut. In the manuscript, an attempt has been made to establish a signaling triad between the Gut, Bone, and the environment to formulate a hypothesis.

Corresponding author: Vibhor Joshi, vibhor.joshi@icmr.gov.in

Introduction: Why This Triad?

A phenotype is a product of genotype and environment. The way we look, the way our organ systems work, is a product of the genes we acquire and the environment we grow up in. Multiple signaling cascades are responsible for producing a single phenotype in living beings [1]. For example, emesis can be caused by overeating, food poisoning, anxiety, or it can be a consolidated effect of all three [2][3][4]. Crosstalk between the signaling cascades plays a key role in maintaining homeostasis. In order to achieve the state of homeostasis, various organs should be able to communicate. Microbes coexisting in the gut have altogether been considered a new organ of the human body [5]. "The gut microbiota" in itself is a dynamic system performing functions that cells of eukaryotic origin cannot perform. Prokaryotic enzymes of microbes can convert ingested substances into products that the human body cannot otherwise produce. These compounds are capable of establishing communication between the gut microbiota and the other organs of the human body [6].

The spectrum of functions that a bone performs gives it the stature of an organ [7]. Bone, being a living tissue, undergoes constant formation and deformation. Apart from support and hematopoiesis, it also plays a crucial role in the storage of minerals [8][9]. Osteoblasts (OB) and osteoclasts (OC) are the cells

responsible for the formation and resorption of bone tissue, respectively. OBs and OCs are the key players in bone tissue engineering (BTE) [10]. The RANK (Receptor Activator of NF–kB)–RANKL (Receptor Activator of NF–kB Ligand)–OPG (Osteoprotegerin) pathway is known to modulate and maintain bone homeostasis [11][12]. An increased number and activity of OCs in bones are responsible for morbidities like osteoporosis and osteopenia [13]. OCs are modified immune cells derived from macrophages. RANKL and M–CSF play a crucial role in the conversion of macrophages into OCs [14].

The Process of Bone Formation and Resorption

Bone is a hard tissue with the primary function of providing support to the human body. It becomes very important for a bone to be in a definite shape to perform its primary function. The bone tissue requires three types of cells. Osteoblasts are capable of inducing sedimentation upon a collagen matrix and ultimately transforming themselves into a lump of calcified osteocytes. A sculpture can be carved out of a stone using a chisel, and bone tissue has osteoclasts (OCs) for redissolving the sedimentations. These are modified immune cells performing a very important function of resorption. Osteoclasts, with the help of hydrolytic enzymes, redissolve the sediments gathered by osteoblasts into the blood and thus resorb the bone. Together, OBs and OCs perform the function of providing a definite shape to the bone that evolution has directed [15][16][17].

The Signaling Pathways Involved in Osteoporosis

Although bone resorption is an important phenomenon, its regulation is even more important. Several pathways and proteins are involved in developing and regulating osteoporosis, namely; omentin-1, TGFβ/Smad pathway, NRF2/Keap1 & mTOR, IP3R & SOCE calcium signaling [18][19][20][21], AMPK signaling, Wnt signaling, orcinol glucoside-mTOR signaling pathway, TRAF-6/MAPK/NF-κB. Chi3L1 decreases in osteoporosis, and AKT3 & RAC1 genes also play a key role, while STK-11 reduces osteoporosis [22][23][24][25][26]. As discussed earlier, a single phenotype can be the result of interactions between multiple signaling cascades.

The Gut Microbiota and the Response It Triggers

Bacteria, among all the other microbes, differ in their ability to inhabit virtually the entire planet, even in extreme environmental conditions such as high mountains (ultralow temperature and atmospheric pressure), volcanoes (ultrahigh temperature), and the bottom of deep trenches in the ocean (ultrahigh pressure) [27]. The gut microbiota is mainly composed of four phyla of bacteria, namely *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* [28].

Since ancient times, it has been known to us that air trapped in the hindgut creates various ailments in our body. From the Ayurvedic perspective, our bodies are composed of *panchbhutas* (five elements); air is one of them. Air (*Vayu/vata*) is responsible for all the motility/movements within our body. It plays an important role in providing mobility to joints and junctions [29][30]. The gut microbiota is a principal creator of metabolites/compounds which otherwise are found nowhere in our bodies. The Short Chain Fatty Acids (SCFAs) manifest mostly immunosuppressive responses by interacting with GPR41, GPR43,

GPR109a, and HDAC inhibition [31]. Alteration in the symbiotic relationship between the hindgut and bacteria is called dysbiosis [32]. This promotes the presence of such microbes which otherwise should not be present in the gut. The presence of *Klebsiella* is highly associated with skeletal joint morbidities. It can make its way through Rho GTPase & PI3K/AKT signaling [33].

Gram-negative bacteria dodge the immune system by modulating the lipid composition of their lipopolysaccharide (LPS) outer membrane. This LPS is involved in triggering various immune responses and is capable of interacting with proteins involved in various signaling pathways. The LPS of most gut microbes is known for its interaction with IL-1B, IL-6, IL-8, TNF-α, MCP-1, TLR-4, and NF-κB [34].

The Role of Atmospheric Pressure (Environmental Component) in Formulating the Triad

Atmospheric pressure is a variable environmental component. High altitude sickness and seasickness are well-known malaises in humans caused due to variation in atmospheric pressure. But the long-term effect of constant atmospheric pressure on the bones and hindgut is not a well-explored area. The HIF-1 (Hypoxia-Inducible Factor – 1) signaling pathway is one pathway that paints a blurry image of the long-term effect of altitude and atmospheric pressure on inflammation, metabolism, vascular tone, and erythropoiesis [35]. All of these phenotypes have a potential effect on the mode of functioning of the gut microbiome and in maintaining bone homeostasis [36][37]. The HIF-1 signaling pathway involves IL-6, IFN-γ, PI3K-AKT, mTOR, TLR4, NFκB, and GLUT signaling, etc. [38][39].

Discussion: Making Sense of the Interactions

NFκB, being a pro-survival molecule, is a strong player in the pathways involved in environmental signaling. It is also involved in inflammation pathways which might be induced by the leakage of LPS from the gut, resulting in autoimmune disorders of bones and joints [40].
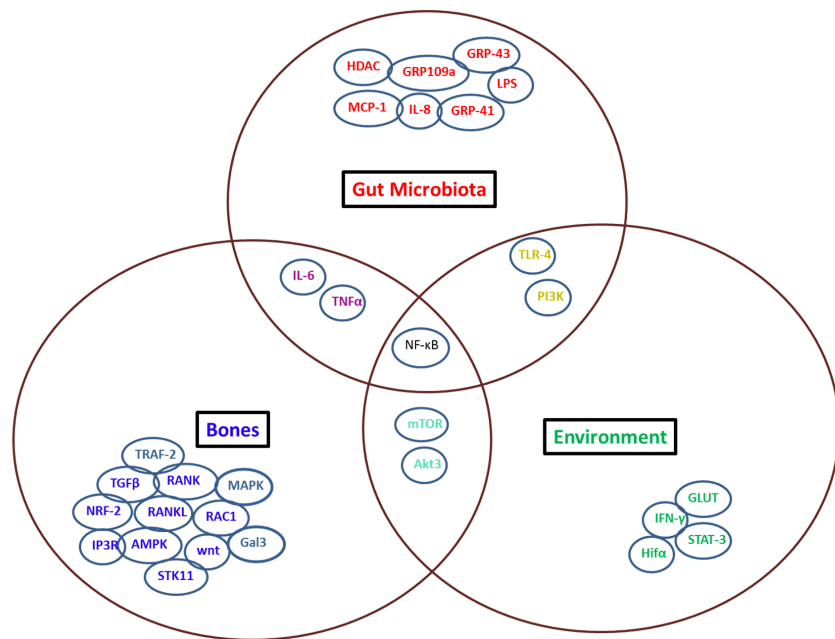
Figure 1. The three poles of the triad and the signaling molecules associated with them are marked with the colors red, blue, and green. The molecules involved with two poles are provided mixed colors of the two poles; for example, molecules involved with Environment (Green) and Gut Microbiota (Red) are colored yellow (TLR-4 and PI3K). NF-κB (black) is involved in all three components of the triad.

At first glance (Figure 1), it might look like a narrative review that pins down the axis of this triad on NF-κB. Although there are other proteins involved, for the sake of making sense of all the interactions, NF-κB lies on the axis if we consider the gut, bone, and the air pressure component of the environment in a triad. The more we know will always be less than what we do not know. Further work will be carried out by the author in this direction, and updated reviews can be expected.

All the mentioned molecules that are involved in signaling are omnipresent if we look at the genotype of individuals. The epigenetic modulations and the interactions among them are highly affected by environmental conditions, and hence the statement "Phenotype is a product of genotype and environment" makes sense. It will also be interesting to see if continuous directional pressure by epigenetic modulation can alter the genotype itself. The time frame for such a study will be of utmost importance.

Statements and Declarations

Availability of Data and Materials: All the data are available in the manuscript, and hence no supplementary data have been provided.

References

1. ^Baye TM, Abebe T, Wilke RA (2011). "Genotype-environment interactions and th eir translational implications." *Personalized Medicine.* **8**:59–70.

2. ^Zhong W, Darmani NA (2017). "Intracellular vomit signals and cascades downst ream of emetic receptors: Evidence from the least shrew (Cryptotis parva) model of vomiting." *Remedial and Clinical Interventions.* **2**.

3. ^Zhong W, et al. (2021). "Mechanisms of Nausea and Vomiting: Current Knowledg e and Recent Advances in Intracellular Emetic Signaling Systems." *International J ournal of Molecular Sciences.* **22**.

4. ^Hu D-L, Nakane A (2014). "Mechanisms of staphylococcal enterotoxin-induced e mesis." *European Journal of Pharmacology.* **722**:95–107.

5. ^Baquero F, Nombela C (2012). "The microbiome as a human organ." *Clinical Mic robiology and Infection.* **18**(Suppl 4):2–4.

6. ^Jandhyala SM, et al. (2015). "Role of the normal gut microbiota." *World Journal of Gastroenterology.* **21**:8787–8803.

7. ^Morgan EF, Barnes GL, Einhorn TA (2013). "Chapter 1 - The Bone Organ System: Form and Function." *In Marcus R, Feldman D, Dempster DW, Luckey M, Cauley JA (Eds.), Osteoporosis. Fourth Edition. pp. 3–20. Academic Press.* doi:10.1016/B978-0 -12-415853-5.00001-7.

8. ^Su N, et al. (2019). "Bone function, dysfunction and its role in diseases including critical illness." *International Journal of Biological Sciences.* **15**:776–787.

9. ^Florencio-Silva R, Sasso GR da S, Sasso-Cerri E, Simões MJ, Cerri PS (2015). "Biol ogy of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells." *B ioMed Research International.* **2015**:421746.

10. ^Amini AR, Laurencin CT, Nukavarapu SP (2012). "Bone tissue engineering: recen t advances and challenges." *Critical Reviews in Biomedical Engineering.* **40**:363– 408.

11. ^Tobeiha M, Moghadasian MH, Amin N, Jafarnejad S (2020). "RANKL/RANK/OP G Pathway: A Mechanism Involved in Exercise-Induced Bone Remodeling." *BioM ed Research International.* **2020**:6910312.

12. ^Boyce BF, Xing L (2008). "Functions of RANKL/RANK/OPG in bone modeling an d remodeling." *Archives of Biochemistry and Biophysics.* **473**:139–146.

13. ^Rettedal EA, Ilesanmi-Oyelere BL, Roy NC, Coad J, Kruger MC (2021). "The Gut Microbiome Is Altered in Postmenopausal Women With Osteoporosis and Osteop enia." *JBMR Plus.* **5**:e10452.

14. ^Inoue K, Ng C, Xia Y, Zhao B (2021). "Regulation of Osteoclastogenesis and Bone Resorption by miRNAs." *Frontiers in Cell and Developmental Biology.* **9**.

15. ^Al-Bari AA, Al Mamun A (2020). "Current advances in regulation of bone home ostasis." *FASEB BioAdvances.* **2**:668–679.

16. ^Franklin M, et al. (2006). "Dried plum prevents bone loss in a male osteoporosis model via IGF-I and the RANK pathway." *Bone.* **39**:1331–1342.

17. ^Ruben JA, Bennett AA (1987). "The evolution of bone." *Evolution.* **41**:1187–1197.

18. ^Wu L, Zhang G, Guo C, Pan Y (2020). "Intracellular Ca2+ signaling mediates IGF-1-induced osteogenic differentiation in bone marrow mesenchymal stem cells." *Bi ochemical and Biophysical Research Communications.* **527**:200–206.

19. △Tang C, Liang D, Qiu Y, Zhu J, Tang G (2022). "Omentin 1 induces osteoblast viability and differentiation via the TGF β/Smad signaling pathway in osteoporosis." *Molecular Medicine Reports*. **25**.

20. △Priddy C, Li J (2021). "The role of the Nrf2/Keap1 signaling cascade in mechanobiology and bone health." *Bone Reports*. **15**:101149.

21. △Jovanovic M, Guterman-Ram G, Marini JC (2021). "Osteogenesis Imperfecta: Mechanisms and Signaling Pathways Connecting Classical and Rare OI Types." *Endocrine Reviews*. **43**:61–90.

22. △Kong C, et al. (2019). "Active Vitamin D activates chondrocyte autophagy to reduce osteoarthritis via mediating the AMPK/mTOR signaling pathway." *Biochemistry and Cell Biology*. **98**.

23. △Zhang L, et al. (2022). "Bioinformatics analysis identification of AKT3 and RAC1 as key genes in postmenopausal osteoporosis." *Experimental and Therapeutic Medicine*. **24**:656.

24. △Canalis E (2013). "Wnt signalling in osteoporosis: mechanisms and novel therapeutic approaches." *Nature Reviews Endocrinology*. **9**:575–583.

25. △Tomomura M, et al. (2015). "Rhinacanthin C Inhibits Osteoclast Differentiation and Bone Resorption: Roles of TRAF6/TAK1/MAPKs/NF-κB/NFATc1 Signaling." *PLoS ONE*. **10**:e0130174.

26. △Park K-R, et al. (2022). "Chi3L1 is a therapeutic target in bone metabolism and a potential clinical marker in patients with osteoporosis." *Pharmacological Research*. **184**:106423.

27. △Medrano-Santillana M, Souza-Brito EM, Duran R, Gutierrez-Corona F, Reyna-López GE (2017). "Bacterial diversity in fumarole environments of the Paricutín volcano, Michoacán (Mexico)." *Extremophiles*. 21:499–511.

28. △Shreiner AB, Kao JY, Young VB (2015). "The gut microbiome in health and in disease." *Current Opinion in Gastroenterology*. **31**:69–75.

29. △Guha A (2007). "Ayurvedic Approach to Rheumatologic Disorders."

30. △Posada E (2021). "The Ayurveda Natural Medicine System and its Environmental Implications." *World Health Organization*. **13**:1–11.

31. △Liu J, et al. (2022). "Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives." *Aging and Disease*. **13**:1106–1126.

32. △Hrncir T (2022). "Gut Microbiota Dysbiosis: Triggers, Consequences, Diagnostic and Therapeutic Options." *Microorganisms*. **10**.

33. △Ebringer A (1989). "The relationship between Klebsiella infection and ankylosing spondylitis." *Bailliere's Clinical Rheumatology*. **3**:321–338.

34. △Candelli M, et al. (2021). "Interaction between Lipopolysaccharide and Gut Microbiota in Inflammatory Bowel Diseases." *International Journal of Molecular Sciences*. **22**.

35. △Hartman-Ksycińska A, Kluz-Zawadzka J, Lewandowski B (2016). "High altitude illness." *Przegląd Epidemiologiczny*. **70**:490–499.

36. △Kumar T, Pandey R, Chauhan NS (2020). "Hypoxia Inducible Factor-1α: The Curator of Gut Homeostasis." *Frontiers in Cellular and Infection Microbiology*. **10**:227.

37. △Behera J, Ison J, Tyagi SC, Tyagi N (2020). "The role of gut microbiota in bone homeostasis." *Bone*. **135**:115317.

38. △Hirai K, Furusho H, Hirota K, Sasaki H (2018). "Activation of hypoxia-inducible factor 1 attenuates periapical inflammation and bone loss." *International Journal of Oral Science*. **10**:12.

39. ^Jantsch J, Chakravortty D, Turza N, Prechtel AT, Buchholz B, Gerlach RG, Bohn E (2011). "Toll-like receptor activation and hypoxia use distinct signaling pathways to stabilize hypoxia-inducible factor 1α (HIF1α) and result in differential HIF1α-dependent gene expression." *Journal of Leukocyte Biology.*

40. ^Camilleri M (2019). "Leaky gut: mechanisms, measurement and clinical implications in humans." *Gut.* **68**(8):1516–1526.

Declarations