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

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Potential competing interests: No potential competing interests to declare.

Comments to the Authors of manuscript entitled “Gut Microbiome, Bone Health, and Air Pressure: Construing the Axis for the Proposed Triad”.

The paper explores the connection between joint pain and changes in weather, particularly focusing on the impact of atmospheric pressure on bones. It raises questions about how factors like HIF and surrounding atmosphere influence bone and gut functions, proposing a signaling triad hypothesis involving the Gut, Bone, and the environment.

1. The introduction effectively highlights the interplay between genotype and environment in shaping phenotypes and emphasizes the importance of signaling cascades in maintaining homeostasis. The example of emesis adds a practical illustration. The mention of the gut microbiota as a dynamic system performing functions beyond eukaryotic cells and its communication with other organs is well articulated.

2. The Process of Bone Formation and Resorption:

The section provides a clear and concise explanation of the bone formation and resorption process. The analogy of a sculpture being carved out of stone using a chisel effectively communicates the roles of osteoblasts and osteoclasts. The involvement of hydrolytic enzymes in bone resorption is appropriately highlighted.

The connection between osteoblasts and osteoclasts in shaping bones according to evolutionary directives is well-established. However, it might be beneficial to expand on the evolutionary aspect for a more comprehensive understanding.

3. The Signaling Pathways Involved in Osteoporosis:

This part introduces various signaling pathways and proteins associated with the development and regulation of osteoporosis. The inclusion of specific pathways such as omentin-1, TGFβ/Smad, NRF2/Keap1 & mTOR, and others provides a detailed overview. The mention of Chi3L1, AKT3, RAC1, and STK-11 genes adds genetic insights into osteoporosis. It would be helpful to provide brief explanations or references for these pathways, allowing readers to delve deeper into specific pathways of interest.

4. The Gut Microbiota and the Response It Triggers:

This section provides a comprehensive overview of the gut microbiota, emphasizing its diverse composition and the

impact of its metabolites on the human body. The reference to ancient knowledge and Ayurvedic perspectives adds historical context to the discussion. To enhance clarity, consider providing brief explanations for the mentioned signaling pathways (IL-1B, IL-6, IL-8, TNF-α, MCP-1, TLR-4, NF-κB) to facilitate readers' understanding.

5. The section of “Atmospheric preassure..” successfully lays the groundwork for the proposed triad hypothesis by elucidating the intricate connections between atmospheric pressure, the HIF-1 signaling pathway, and the gut-bone interplay.

6. Making Sense of the Interactions:

This section provides a comprehensive interpretation of the interactions within the proposed triad, with a focus on the pivotal role of NFκB as a pro-survival molecule. The connection between NFκB and environmental signaling, particularly in the context of inflammation pathways induced by LPS leakage from the gut, is effectively established, contributing to a nuanced understanding of potential autoimmune disorders affecting bones and joints. this section effectively synthesizes the complex interactions within the proposed triad, placing NFκB at the forefront, and sets the stage for further exploration and refinement of the triad hypothesis.

I recomment minor correction.