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 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. 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. 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 leakage of LPS from the gut, resulting in autoimmune disorders of bones and joints [40].
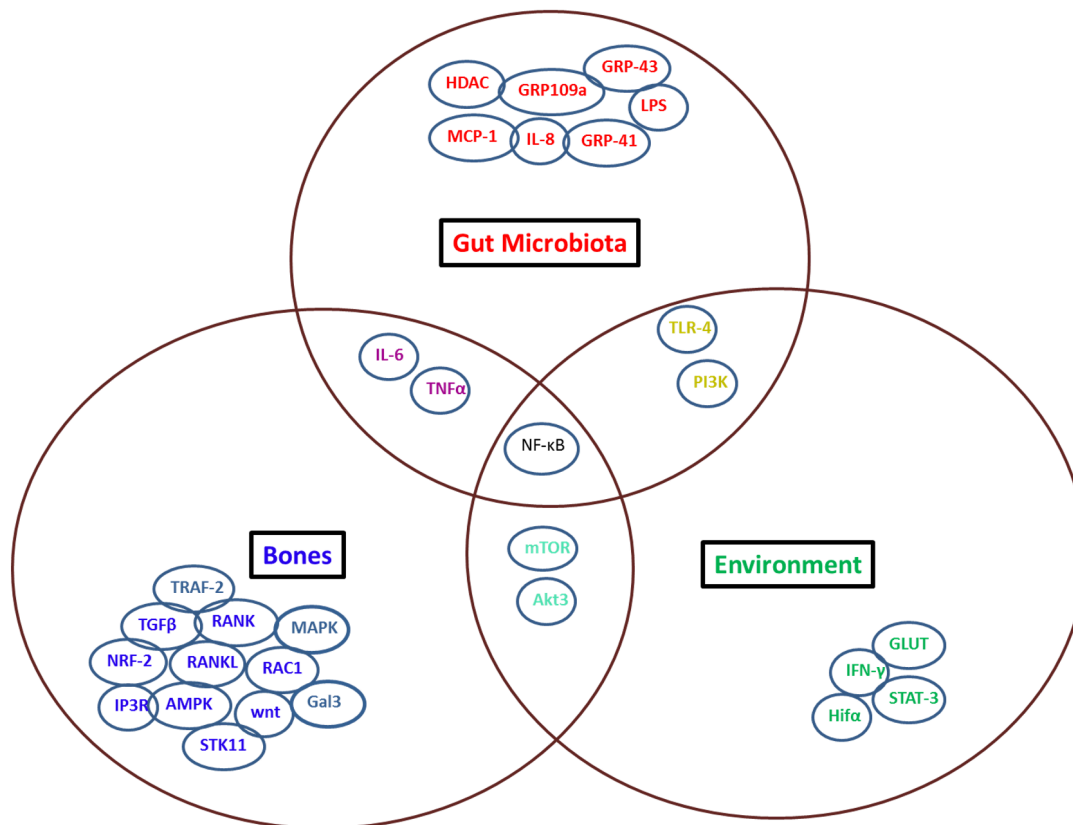
Figure 1. The three poles of the triad and the signaling molecules associated with them are marked with the colors red, blue, and green. The molecules involved with two poles are provided mixed colors of the two poles; for example, molecules involved with Environment (Green) and Gut Microbiota (Red) 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

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Declarations