Can We Improve Bone Regeneration?

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Ever fractured a bone before? Or know someone who did? Many of us overlook the amazing fact that our body is able to regenerate bone lost during a break. Depending on the severity of the fracture, our cells can create and send signals to increase the production of bone cells that will eventually heal our fractured bone! However, there are many things that can impact our bone's regenerative capabilities, including diabetes, low vitamin D levels, poor nutrition, and smoking. Something inevitable like aging also causes bone regeneration to significantly slow down. If our body cannot regenerate simple fractures, it can cause a multitude of different problems, including decreased mobility. So how can we figure out a way to create a therapy where we can promote and speed up bone regeneration? To answer this question, it is important for us to first know some of the background information related to finding a solution.

When talking about anything related to the bone, there's a bit of terminology to first understand. An osteoblast is the name of one type of bone cell. Osteoblasts are derived from mesenchymal stem cells (MSCs)—basically, MSCs turn into osteoblasts. MSCs come from the bone marrow, and when they are made, they receive different signals from the cells around them that give that give them molecular instructions to turn into (i.e., differentiate) a specific cell type; in this case being an osteoblast. But as stated earlier, there are plenty of different reasons that could lead to osteoblast formation/regeneration being slowed down or even stopped. Because MSCs are constantly being made and, therefore, typically present in high amounts, one possible explanation for the lack of osteoblast production is that the signals needed to turn the MSCs into osteoblasts are the problem. Because if the signals are not present or strong enough, MSCs cannot turn into osteoblasts, which would cause bone regeneration to slow down.

Given this information, the focus shifts to the specific signals that cause MSCs to differentiate into osteoblasts. Cells constantly create molecules called proteins. One of the many functions of proteins is to act as signals that can "tell" a cell to do something. Some of the most important signals that play a role in turning MSCs into osteoblasts comes from the Wnt family of proteins. Within this family, there are many different types of Wnt proteins that act as signaling molecules. Specifically, three important Wnt proteins— Wnt4, Wnt5a, and Wnt9a— have been found to be highly present in a disease called fibrous dysplasia, where patients have significantly increased bone mass. Due to the evidence that these Wnt proteins have a role in increasing bone volume, we are interested in creating a therapy involving cells that produce high levels of the Wnt proteins that could be injected into fibrous dysplasia patients. We hope that these injected cells will help differentiate naturally-occurring MSCs in the patients into osteoblasts in order to promote bone regeneration.

To create this therapy, we first need to look at what overexpressing the Wnt proteins will do to the MSCs themselves. There are three different criteria to assess when researching the impact of over-expressing Wnt proteins in MSCs: proliferation, differentiation, and cell migration.

Proliferation refers to how quickly cells divide to give rise to new cells. In this case, we will look at the impact that increasing these three specific Wnt proteins will individually have on MSC proliferation. Due to the role that these signaling proteins may have in fibrous dysplasia, we expect that proliferation will be increased compared to cells that do not have increased Wnt. In this context, differentiation refers the process of MSCs turning into other cell types after receiving the Wnt signals. MSCs can turn into a variety of different cell types; however, our hope is that the Wnts will cause MSCs to differentiate into osteoblasts. Other research has indicated that MSCs typically differentiate into osteoblasts in the presence of these Wnt signals, but we want to know whether or not having increased Wnt produces a different effect. Finally, cell migration refers to how well cells can migrate (move) from one place to another, which is important because we want the MSCs to be able to migrate to the site of a wound (i.e., bone fracture) in order to help heal the bone. We hope to not observe a decrease in cell migration. If results are as expected, we can continue with our line of experiments and hopefully come closer to creating a stem cell-based therapy for fibrous dysplasia.

References

Monroe DG, McGee-Lawrence ME, Oursler MJ, Westendorf JJ. (2012) Update on Wnt signaling in bone cell biology and bone disease. *Gene.* 492(1),1-18. 10.1016/j.gene.2011.10.044. PMID: 22079544; PMCID: PMC3392173.

Musiał-Wysocka A, Kot M, Majka M. (2019) The Pros and Cons of Mesenchymal Stem Cell-Based Therapies. *Cell Transplant.* 28(7), 801-812. 10.1177/0963689719837897. PMID: 31018669; PMCID: PMC6719501.

Thomas S, Jaganathan BG. (2022) Signaling network regulating osteogenesis in mesenchymal stem cells. *J Cell Commun Signal.* 16(1), 47-61. 10.1007/s12079-021-00635-1. PMID: 34236594; PMCID: PMC8688675.

Yu Bo, Chang J, Liu Y, Li J, Kevork K, Al-Hezaimi K, Graves DT, Park NH, Wang CY. (2014) Wnt4 signaling prevents skeletal aging and inflammation by inhibiting nuclear factor-κB. *Nat Med.* 20(9):1009-17. 10.1038/nm.3586. PMID: 25108526; PMCID: PMC4159424.