Unlocking FD/MAS

By Ruth Hernandez

What is FD/MAS?

Fibrous Dysplasia (FD) is a rare bone disorder that typically manifests itself during early childhood resulting in abnormal bone growth[1]. FD is caused by mutations in the GNAS gene, leading to overactive signaling in bone cells[2]. FD can occur by itself or alongside McCune-Albright syndrome (MAS), which includes skin spots and hormone imbalances[2]. There is an urgent need to come up with potential treatments for this disease that will reduce lesion expansion and disease progression.

Gsα Mutations and Their Impacts on Bone Balance

In FD/MAS there is a change in the GNAS gene that makes a protein called Gsα overly active. Think of Gsα as a lock that fits into specific keys that help turn on different processes within the cell. Normally, Gsα has a specific lock shape that allows it to work properly. However, in this condition, a mistake has been made in the set of genetic instructions for making our "normal" Gsα lock. This mistake causes a small piece of the Gsα lock to be different. As a result, the Gsα lock does not fit into its keys correctly leading to problems within the cell.

Our Gsα protein "lock" behaves in a switch-like manner that helps our cells respond to signals from other molecules. When Gsα is too active due to mistakes made in its genetic instructions, it gets stuck in the 'on' position. Being stuck in the 'on' position causes Gsα to constantly send signals inside the cell. This continuous signaling leads to the overproduction of another molecule called cyclic adenosine monophosphate (cAMP). cAMP acts like a messenger, triggering a series of events that activate other proteins in the cell. In FD/MAS, elevated cAMP levels disrupt signaling cascades, leading to the misdirection of osteoblasts and osteoclasts, two crucial cell types responsible for maintaining bone balance (homeostasis).

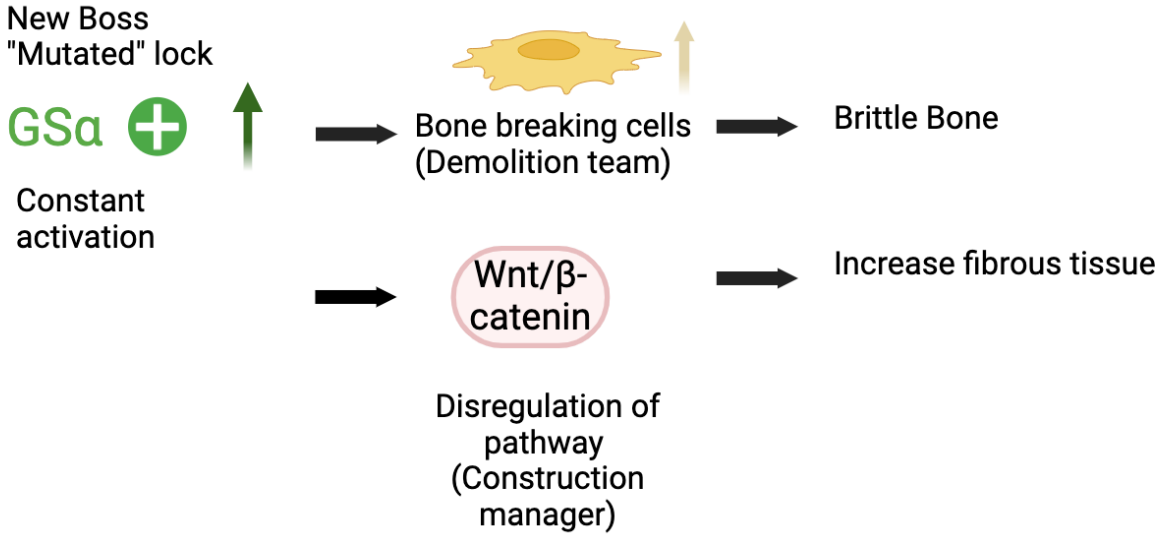
The constant activation of Gsα protein interferes with the way that bone cells communicate. It disrupts the normal process of how bones grow and change. As a result, people with FD/MAS may have abnormal bone growth, changes in how dense their bones are, and problems with how their bones remodel (or rebuild) themselves[2].

Signaling Pathways Disrupted by Mutant Gsα

Now, imagine your body as a well-coordinated team building a house (bone tissue). The Wnt/B-catenin signaling pathway serves as a project manager who oversees the construction of the house and makes sure everything is in order. The mutant Gsα lock from my previous analogy is now a new boss that the site has hired. This new boss starts coming in and is giving overly enthusiastic instructions. This disrupts the project manager's (Wnt/B-catenin pathway) plans and causes the bone-making workers (osteoblasts) to start building the house with the wrong materials! This disruption in the

Wnt/β-catenin pathway leads to the formation of fibrous tissue instead of normal bone[5].

Our new Gsα boss also affects another worker, RANKL, whose job is to signal to the demolition team (osteoclasts) to break down old bone tissue when it is necessary[1]. The hyperactivity of our new Gsα boss causes RANKL to get mixed signals and can't communicate with the demolition team which leads to confusion and improper breakdown of bone. In FD/MAS this dysregulation causes more bone to be broken down at a higher rate than bone is being made leading to bone fractures[1].



Treatment Limitations

Currently, there is no effective way to treat FD/MAS, highlighting the urgent need for better therapies that can prevent FD lesions from worsening. Patients often undergo numerous surgeries to manage fractures which are costly. Denosumab, a treatment that slows down bone breakdown by osteoclasts, shows promise but can lead to increased bone turnover once it is discontinued[1]. Bone turnover is the natural process where old bone is broken down and replaced with new bone, helping keep bones strong and healthy. If there is an increase in bone turnover, that means that bone-breaking cells exceed the rate of bone-making cells which causes weak and brittle bone to form. Bone-strengthening medications known as bisphosphates offer pain relief but do not address the underlying issue of FD lesion growth and disease expansion[2].

Future Directions: Combating Treatment Limitations

Despite the challenges posed by FD/MAS, ongoing advancements in treatments offer hope. Researchers have identified the main problem in FD/MAS as the high levels of cAMP and Wnt signaling, suggesting that targeting these pathways could lead to

effective treatments. The Hoffman and Fierro labs are collaborating to find new treatments. The Hoffman Lab at UCSF used a system to find 41 effective compounds that might stop the cAMP pathway from working. The Hoffman lab tested these compounds on yeast cells that modeled FD/MAS. They found that these compounds reduced cAMP levels, which is a good sign for potentially treating FD/MAS.

The Fierro lab created a lab model of FD/MAS using bone marrow-derived mesenchymal stromal cells (MSCs). MSCs are a type of stem cell that can develop into various tissues including fat, cartilage, and bone. By introducing FD mutations into these stem cells, the Fierro lab was able to mimic FD/MAS characteristics, including high cAMP levels and issues with bone cell maturation. Their goal is to use this model to identify the most promising compounds that will inhibit the dysregulation observed in FD patients. These compounds will be further tested on mouse models of FD/MAS to see the effects of these inhibitors inside a living organism rather than on a petri dish.

This research is not only exciting for regenerative medicine but also for understanding how the body heals itself. The Fierro lab's ability to turn patient stem cells into FD/MAS models in the lab could lead to personalized treatment plans. By focusing on specific disrupted pathways in FD/MAS, like the cAMP pathway and Wnt/β-catenin signaling, they aim to develop treatments that could stop the progression of this condition. Future research directions include testing these compounds in animal models and eventually in clinical trials, with the hope of providing effective therapies for FD/MAS patients.

References

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