Loss of a carbohydrate modifying enzyme shifts bone formation into overdrive

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Glucuronyl C5 epimerase (Hsepi) is an enzyme that modifies Heparan sulfate (HS). HS is a negatively charged carbohydrate chain that is present in virtually all the animal tissues. The chain consists of a repeated disaccharide with an N-acetylglucosamine (GlcNAc) and a glucuronic acid (GlcA). Hsepi modifies the HS chain by converting GlcA into iduronic acid (IdoA).

If the Hsepi gene is removed from an animal (Hsepi knockout), then there is no conversion of GlcA to IdoA. This resulted in HS chains that completely lack IdoA and abnormalities in many organs in mice. It does not allow the bone to develop properly and causes various problems in eyes, kidney and lungs. These mice die shortly after birth.

Many signaling proteins can bind to HS and activate so called signaling pathways. In these pathways, many interactions take place among many downstream proteins, which ultimately triggers specific changes in the cell. In normal cells with Hsepi, HS disrupts a specific signaling pathway for bone formation by binding with Bone Morphogentic protein 2 (BMP2).

BMP2 are the growth factors which belong to the TGF-β superfamily. These TGF-β proteins play major role in the formation and development of cartilage and bones. The interaction between HS and BMP2 leads to removal of BMP2 and thereby preventing it from interacting with growth factor receptors and following activation of bone formation.

In this study, BMP2 signaling in fibroblast cells from mice embryos lacking Hsepi were studied. These embryonal cells were chosen based on their qualities as a great model system for BMP2 signaling and being easy to grow. Also, large number of the required cells can be obtained from the single embryonal colonies. The BMP2 pathway was studied by analyzing the amount of activated proteins like Smad 1/5/8. The Smads are the downstream proteins that transfers outside signals from the TGF-β ligands to the nucleus where the particular gene expression is activated. The BMP2 signaling was found to be enhanced in knockout cells when compared to wild type cells. There is also increased phosphorylation of Smad 1/5/8 in the knockout MEF cells.

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