**Importance of SPH2 in RAS/MAPK signalling pathway in NF1 nondystrophic scoliosis**

1. Introduction:

Neurofibromatosis is one the most common autosomal genetic disorder that is characterized by the growth of noncancerous tumors called neurofibromas. Neurofibromatosis has been classified into two distinct type: NF1 and NF2. We will choose to focus on the more common type; NF1 which is usually diagnosed during childhood and affects more than 100,000 people in the United States and every 1 in 4000 people. Neurofibromatosis is caused by a mutation on the NF1 gene which is located on chromosome 17,this gene codes for the neurofibromin protein. The neurofibromin protein regulates the activity of another protein called the RAS, however the mutation leads to a disruption in this train of regulation. The mutation on the NF1 gene results in a shortened version of neurofibromin being produced that cannot bind to RAS or regulate its activity, resulting in a more active RAS. Cells are provided with the instructions to begin dividing but never told when to stop, leading to abnormal cell division and the formation of tumors. NF1 is characterized with several secondary symptoms as well that can affect the brain, spinal cord, nerves and skin. The severity and type of secondary symptoms widely vary from patient to patient. Secondary symptoms range from distinctive café au lait spots, as well as freckles to non cancerous tumors called neurofibromas, high blood pressure, bone defects, scoliosis (curvature of the spine), learning disabilities, Lisch nodules (benign growths on the iris of the eye), and optic gliomas (benign tumors on the optic nerve that connects the eye to the brain). A great deal of of research has been conducted on the pathogenesis of the peripheral and central nervous system tumors that affect NF1 patients. However, there isn’t much focus or research on understanding the molecular mechanisms of several secondary non-malignant symptoms, specifically the skeletal manifestations that affect upto 50 % of NF1 patients. The orthopedic bone manifestation fall into three main categories: kyphoscoliosis, pseudarthrosis, and disorders of bone growth. The most prevalent skeletal manifestation amongst NF1 patients is kyphoscoliosis, which affects up to 35% of NF1 patients. Kyphoscoliosis is a term that refers to the pathological curvature of the spine, it usually begins to form and is mostly diagnosed in young school age children, is extremely deforming, and requires multiple surgeries to prevent further secondary morbidities such as lung disease and disfigurement. Scoliosis associated with NF1 can take two forms: dystrophic and nondystrophic scoliosis based on radiographic evaluation. The dystrophic form has distinguishable features that include a curve that is thoracic kyphoscoliosis and a sharp angular curve with distorted ribs and vertebrae. Nondystrophic scoliosis is classified by being compared to idiopathic scoliosis. It has similar presentations, curvatures, physical resemblance as well as diagnosis to idiopathic scoliosis. We want to take the physical and genetic resemblances between the two types of scoliosis and apply it to treating nondystrophic scoliosis using similar techniques and procedures. The article that is central to our research here was conducted by Kim et al (2013), who speculated that a deficiency in SHP2 in chondrocytes leads to severe scoliosis in mice, and an activation of Shp2 leads to a positive effect on the RAS/MAPK signal transduction. SHP2 is a positive regulator of RAS-MAPK signaling, which is essential for normal skeletal growth. Human mutations involving the RAS-MAPK signaling pathway have been described with skeletal abnormalities, including scoliosis and kyphosis. Protein-tyrosine phosphatases nonreceptor type 11 encodes SHP2 (Src homology-2)-containing protein tyrosine phosphate. Protein-tyrosine phosphatases nonreceptor type 1, plays a central role in RAS/MAPK signaling downstream of several receptor tyrosine kinases including epidermal growth factor receptor and fibroblast growth factor receptor. 1 In general, an activation of SHP2 has a positive effect on the RAS/MAPK signal transduction as described by Kim et al (2014). Furthermore , as described in Chen et al (2008) NF1 cells have the ability to be expressed in osteoblasts as well as chondrocytes make them a good candidate for targeted deficiency of SPH2. So thus we will proceed with the experiment speculating similar results as Kim et al (2013) based on the similar RAS/MAPK pathways expressed in both NF1 and idiopathic scoliosis and the ability of NF1 cells to differentiate into chondrocytes.

**II. The Experiment:**

The specific aim of this experiment is to show the importance of SPH2 in RAS/MAPK signalling pathway in NF1 and the effects of SPH2 deficiency on nondystrophic scoliosis using genetically engineered mice. We used the same the mouse model generated by Kim et al (2013)as it is the first mouse model of its kind to be genetically engineered and geared towards kyphoscoliosis. We generated genetically engineered mice with inducible deletion of the Shp2 in chondrocytes. SHP2 was inactivated in chondrocytes in the growth stage from mouse age of 4 weeks. Radiographical, micro-computed tomographical, and histological assessments were used to analyze that the changes in the spine. It is hypothesized that we would generate similar results as Kim et al (2013) showing that once you knock out SHP2 in chondrocytes it leads to the scoliosis worsening. This shows that there is a direct correlation between the deficiency of SHP2 and scoliosis in NF1 nondystrophic scoliosis.

**III. Discussion:**

We have determined from the experiment above that SHP2 is a positive regulator of RAS-MAPK signaling.This mouse model is an important tool to study how the SHP2 deficiency affects RAS-MAPK signaling in NF1 specific nondystrophic scoliosis and how it worsens when the RAS-MAPK signaling is not regulated.

**IV. References:**

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# J.M. Friedman, Epidemiology of neurofibromatosis type 1

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