Name(s)

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Project Number

S1201

Project Title

Identification of Treatments for Hemophilic Joint Disease through Evaluation of Vascular Defects

Abstract

Objectives

Hemophilia A, or FVIII deficiency, is characterized by spontaneous bleeding in weight-bearing joints, resulting in a debilitating orthopedic complication called hemophilic arthropathy (HA). Bleeding causes inflammation and hypoxia which induces angiogenesis. Despite advances in treatment, HA still continues to develop. The goal of this project was to identify alternative treatment targets and a treatment for hemophilia that prevents vascular abnormalities.

Methods

The goal was approached by developing insight into the formation of abnormal blood vessels, identifying multiple angiogenic markers expressed in FVIII KO models to serve as treatment targets, and testing the efficacy of the most promising anti-angiogenic treatment candidate targeting Vascular endothelial Growth Factor (VEGF).

Results

It was determined that anti-VEGF significantly reduced aSMA positive vessels at week 2, but increased hypoxia. These results were validated with vascular casting. It was also discovered that abnormal blood vessels is specific to hemophilia as compared to rheumatoid arthritis and osteoarthritis. It was confirmed in mice that the new vessel formation and vascular remodeling was increased in hemophilia (FVIII KO) mice after bleeding, but not to the same extent in wild type mice subjected to joint bleeding. It was determined that lack of hemostasis is driving excessive vascular changes. Finally, multiple angiogenic targets were identified in the mouse hemophilic joints after bleeding.

Conclusions

This project provided insight into the formation of abnormal vasculature in HA. Multiple angiogenic markers were identified, providing potential treatment targets. It was discovered that anti-VEGF treatment significantly reduces aberrent vasculature. It was established that FVIII deficiency drives aberrant vasculature in hemophilic joint disease as compared to bleeding. In addition, various imaging techniques were developed/optimized to analyze blood vessels in the joints.

Summary Statement

Antibody treatments were identified for hemophilic joint disease, the cause of the development of hemophilic arthropathy was discovered, and the changes in vasculature were analyzed via the optimization of imaging techniques.

Help Received

Dr. Tine Wyseure and Dr. Laurent Mosnier mentored me by providing their insight and teaching me. Dr. Robert Sah and Dr. Saeed Jerban did the microCT scans. Dr. Annette von Drygalski and Dr. Martin Lotz provided the clinical samples. Genentech provided the anti-VEGF antibody.