THE ROLE OF SMYD1 IN CARDIAC DISEASE

Ludovica Farese (Sarah Franklin)

Department of Internal Medicine – Cardiovascular Medicine Division

Cardiovascular disease (CVD) is the leading cause of death globally. In 2012, an estimated 17.5 million people died from CVDs, representing 31% of global deaths. Therefore, understanding how the heart functions at a molecular level is essential in order to find a cure for these diseases.

Smyd1 was originally identified as a myocyte-specific methyltransferase important in the regulation of cardiac development, however, its role during adult disease is completely unknown. Our preliminary data in cardiac-specific knockout mice have shown that loss of Smyd1 in the adult heart leads to cardiac dysfunction and ultimately heart failure. In addition, we have shown that overexpression of Smyd1 in isolated cells inhibits hypertrophic growth, a precursor to heart failure. Given this preliminary data my hypothesis was that overexpression of Smyd1 could inhibit cardiac disease in an animal model through its methyltransferase activity. To investigate this hypothesis I have carried out two main types of experiments to study the function of Smyd1 in the heart. First, I have analyzed cardiac tissue which overexpresses Smyd1 after isoproterenol-induced heart disease. I have imaged these tissue sections, stained with H&E or trichrome, and analyzed the degree of fibrosis, hypertrophy and chamber dilation. Second, I characterized Smyd1 binding proteins through immunoprecipitation and western blotting to identify Smyd1 methylation targets and determine how this protein affect heart function at a molecular level. My experiments showed that Smyd1 interacts with adenylosuccinate synthase (ADSS) in both skeletal muscle and cardiac cells. These results suggest that Smyd1’s ability to regulate cardiac growth may be carried out through the metabolic remodeling of purine metabolism in the normal and disease heart.

These exciting results have enabled me to characterize Smyd1’s in vivo function and will ultimately allow us to determine its potentially as a therapeutic target for cardiac disease.