Immunogenic glycans and antibody glycosylation: Insights into bioprosthetic heart valve deterioration

Malak Hariri

Supervisor: Prof. Vered Padler Karavani

Cardiovascular diseases are the leading cause of death worldwide, and heart valve disease is a common condition. The primary treatment is valve replacement using synthetic heart valves which are classified into two types: mechanical heart valves (MHVs) and bioprosthetic heart valves (BHVs). BHVs contain the immunogenic glycans *N*-glycolylneuraminic acid (Neu5Gc) and galactose-α1,3-galactose (αGal) which elicit antibody (Ab) responses. Recent studies have shown that IgG Abs against these glycans are induced as early as one-month post-implantation and contribute to BHV calcification. Additionally, other studies suggest that the glycosylation of circulating serum Abs is altered in inflammatory conditions. We hypothesize that IgM isotype may participate in BHV calcification, and that glycosylation of serum Abs is altered in BHV recipients, reflecting inflammatory responses that contribute to BHV calcification. We investigated anti-glycan IgM responses and serum Abs glycosylation in a large cohort of BHV recipients (n=455) compared to control patients with MHV or coronary artery bypass graft (n=96) at multiple timepoints (M0-M24). Ab glycosylation was assessed using printed glycan microarrays using lectins, HILIC-UHPLC, and mass spectrometry. Additionally, human and mouse anti-glycans IgGs engineered with distinct glycosylation patterns were used to examine effects of immune cell activation in vitro. ELISA analysis indicate that anti-glycans IgM levels are not significantly different between BHV patients and control patients. Glycosylation profiling revealed consistent patterns across the different technologies, identifying core-fucosylated, sialylated, galactosylated, and mannose terminated N-glycans. Together, these findings suggest that IgG glycosylation may represent valuable biomarker for monitoring early calcification in BHV recipients.