Principal Investigator: Rony Dahan
Grant Title: Effect of IgG Fc glycome on cancer immunity

Abstract:

Objectives: The Fc domain of antibodies, which mediates antibody effector functions, exhibits great heterogeneity due to the different combinations of the IgG subclass and the specific glycoform attached to the Fc. These different glyco-protein structures can mediate diverse immune responses due to their differential binding profile to the different Fc receptors. We hypothesize that the Fc glycan fingerprint of IgG antibodies is an important determinant that shapes their response during malignancy. We aim to identify Fc structures associated with cancer. Next, with the use of murine models we aim to gain enhanced mechanistic insight into the tumor immunity mediated by the different Fc structures, while focusing on their engagement of different Fc receptor effector pathways.

Methods: In order to obtain a subclass specific Fc glycosylation pattern for each individual we established a mass spectrometry based assay to determine this structure. This assay was established for both human and for mice samples. The process includes obtaining plasma samples from individuals inflicted with cancer and isolation of IgG molecules. Next, the IgG molecules undergo tryptic digestion followed by enrichment with HILIC (Hydrophilic interaction chromatography) for glycopeptides. Samples are then analyzed using a Fusion Lumos Mass spectrometer. For bioinformatics data analysis, glycopeptides are identified using Byonic (Protein Metrics) and quantified using Skyline (MacCoss).

Results: We were able to determine the Fc fingerprint of healthy individuals and of naive wild type C57Bl6 mice. Next, we characterized the unique Fc fingerprint of treatment-naïve patients suffering from advanced Non-Small Cell lung cancer (stages IIIb-IV). These patients show a distinct IgG Fc glycosylation pattern, specifically, a decreased galactosylation pattern across all types of IgG subclasses. Next, we characterized the Fc fingerprint of mice using a B16 tumor model. Here, we also observed a unique Fc fingerprint of mice inflicted with cancer, although to a lesser extent compared to the human disease.

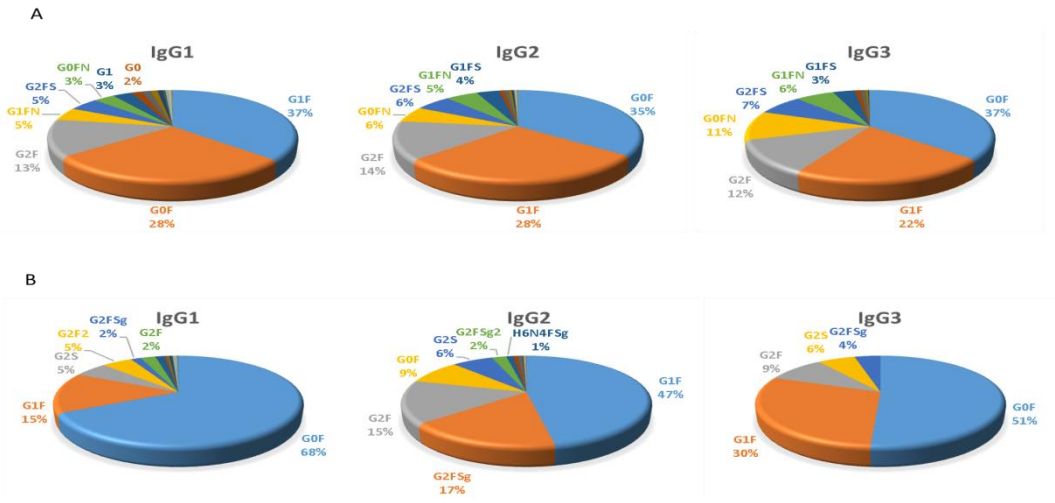

Figure 1. Subclass specific IgG Fc glycan distribution a healthy human (A) and naïve wild type C57B6 mouse (B)