Metabolic profiling of human PBMC subsets

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Immunomodulatory therapies, such as those used to treat cancer or autoimmune conditions, typically target antigen receptor, co-receptor, or cytokine function. However, it is becoming more and more evident that efficient and accurate immune manipulation will undoubtedly include targeting of basic biological pathways as well. Indeed, the growing field of immune metabolism has uncovered a plethora of examples that highlight dynamic metabolic programs throughout immune responses, as well as functional defects in response to metabolic substrate or pathway restriction. There is now a need to translate these findings to human immunotherapies, which will require methods to assess human immunometabolic function.

Our objectives were: 1) to assess the application of extracellular flux technology as a means to assess the metabolic profile of multiple immune cell types from either fresh or cryopreserved biorepository sources; 2) to test whether this technology could discern immunometabolic differences from individuals with type 1 diabetes (T1D) from controls.

Our results showed robust metabolic activity in response to specific activation of enriched B cell, monocyte, and T cell subsets. Importantly, cryopreserved cells maintained their metabolic responsiveness and were actually more responsive to TLR stimulation. When the assay was applied to our clinical cohort, we found that T cell respiration after TCR activation was decreased in T1D as compared to controls. Furthermore, donors carrying the autoimmune risk allele of protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*) displayed a decreased glycolytic shift after TCR activation. Finally, we found T cell respiratory capacity to correlate with age in donors until 30 years of age, which is indicative of an increased proportion of memory T cells. After age 30, T cell respiratory capacity is inversely correlated with age, possibly signifying the onset of immune senescence. These findings highlight the application of extracellular flux technology to assess human immunometabolic profiles, which will facilitate the discovery immunotherapies that target metabolic pathways. Further, the capacity to identify immunometabolic associations with disease states bears important implications for biomarker discovery.