Principal Investigator: Estela Jacinto
Grant title: Regulating T cell receptor diversity by the hexosamine pathway

Abstract

The ability to mount an immune response to pathogens relies on a diverse TCR repertoire. During early T cell development in the thymus, the TCR chains are formed by somatic rearrangements of the Variable (V), diversity (D), and joining (J) gene segments together with random addition or deletion of nucleotides, thus generating tremendous variety of TCRs. The pairing of α and β or γ and γ chains, during the development of αβ- or γδ-T cells, also add another layer of diversification. While many studies have addressed the genetic mechanisms and regulation of this process, little is known as to how nutrients and metabolism contribute to generating TCR diversity. Although some studies have suggested that diet affects the immune system, the molecular basis for the effects of specific nutrients in immunity remains unexplored. Therapeutic strategies that rely on pharmacological manipulation of signaling and metabolic pathways are currently the methods of choice for the treatment of a variety of diseases. However, our expanding knowledge on the interplay between genes and nutrient metabolism could be exploited to develop better strategies that utilize diet manipulation for treatment, by itself or in combination with pharmacological compounds.

Our findings unravel how the de novo hexosamine biosynthesis pathway (dn-HPB) is required for early T cell development due partly to its role in providing UDP-GlcNAc that is required for *N*-glycosylation of the αβ- and γδ-TCR. We generated mice that have specific deletion of GFAT1, the critical enzyme required for dn-HBP. Our studies will address how T cell receptor diversity could be dependent on dn-HBP during T cell development in the thymus. We will investigate how specific nutrients reprogram metabolism when hexosamine production is defective and how this metabolic reprogramming leads to impaired TCR diversity. Our studies have significance for defining how nutrients affect the generation of a diverse TCR repertoire that is crucial for a robust immune system. They will also provide insights on how poor diet affects immunity due to impaired hexosamine biosynthesis.