Effects of causative Calreticulin mutations in Essential Thrombocytosis on cytokine production and MHC class I antigen presentation.

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PROJECT SUMMARY/ABSTRACT

The majority of the human myeloproliferative disorders (MPD) are caused by an acquired somatic mutation that affects the cells that derive from myeloid hematopoietic progenitor cells. This group of disorders includes Essential Thrombocythemia (ET), which is characterized by an increment in platelet count and neutrophil dysfunction, persistent thrombocytosis and an increment in cytokine production. Mutations in MPL exon 10, CALR exon 9, and JAK JAK2V617F (JAK2) have been shown to be mutations related to ET phenotype. Independent studies using different populations have revealed that MPL exon 10 mutation is responsible for the 5% of ET cases, JAK2 for the 56% and CALR for the 25%. Because previous studies that focused on elucidate the physiological difference among mutational status of ET patients just take into account the presence or absence of the most common ET mutation, JAK2, the relation between ET genotype (CALR, JAK2 or MPL) and its physiological effects represents a critical challenge. Studies looking to dissect the relationship between mutational status and cytokine profile have shown that although cytokines expression levels and growth factors are significantly increased in ET patients, cytokine profiles differ between JAK2 positive and JAK2 negative. Unfortunately, independent researchers have found different cytokine profiles, possibly because MPL and CALR mutations were not considerated as a different mutational status.

Because mutational background could affect the cytokine profile of MPD patients, and any contemporary study has emphasis on this issue, my research project will focus on identify if Calreticulin ET genotype affect cytokine profile and MHC class I antigen presentation. We hypothesize that cytokine profile will differ by ET genotype. To test this hypothesis we will pursue the following lines of inquiry (1) Determine if Puertorrican population have the same mutational ET proportions as previously reported populations of Europe, China, and Austria using peripheral granulocytes DNA sequencing. (2) Identify the cytokine profile by ET mutational status using cytokine beads. (3) Determine if ET Calreticulin mutation affects MHCI antigen presentation using CRISPR-Cas9 system and epitope detection.

The achievement of these aims will enhance the characterization of patients to improve prognosis and treatment.