Molecular and Genetic study of Myeloma
Epigenetic Contributions to Multiple Myeloma Pathogenesis

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Overview

• Multiple myeloma is a plasma cell malignancy characterized by cellular resistance to apoptosis, a genetically programmed cell death process, leading to prolonged survival and accumulation of tumor cells in the bone marrow microenvironment

• Standardized incidence rates of MM are typically two-fold higher among African Americans compared to European Americans, and higher among men

• The etiology of MM and differences by race and sex are unclear

• Although, evidence from family studies of two or more affected first-degree relatives, high concordance among monozygotic twins and candidate gene- association studies suggest a genetic component, inherited alterations in DNA sequence alone is insufficient for disease causation
Hypothesis

Epigenomic modification in DNAm profiles is associated with altered risk of MM and among patients with MM, modifications in DNAm contribute to the excess risk observed among African Americans.
Overview, II

• Using a genome-wide approach, we capitalized on a unique opportunity to explore epigenetic relationships in DNA from unfractionated peripheral blood as well as CD138+ tumor cells from the bone marrow microenvironment obtained from ethnically diverse, well-characterized populations of MM while taking advantage of recent advances in human genome sequencing.

• Our systematic unbiased approach to evaluate modifications in DNAm by evaluating the entire epigenome, analogous to GWAS of common variants, will advance our understanding of this common complex disease.

• Modeling the influence of epigenetic changes on MM pathogenesis is a critical step toward characterizing the epigenotype-phenotype as well as epigenotype-genotype (mQTL) relationships that may be dimorphic by race/ethnicity.
iMAGE Study of Myeloma

- iMAGE is an ongoing multi-site hospital-based case-control study designed to examine the effects of biological, chemical, physical, social and genomic influences on the development and progression of MGUS to MM, which may differ by African American and European American race/ethnicity

- iMAGE – April 2009 to present (phase I ends fall 2012)

- Questionnaire was designed for future pooled analyses with concurrent and existing case-control studies of MM included in the International Multiple Myeloma Consortium

- Clinical and genetic phenotyping

- Biospecimens include: sera, plasma, buffy coats, EBV cell lines, saliva, CD138+ plasma cells from bone marrow

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DNAm Signatures in Cases and Controls

We demonstrate clear differences in DNAm signatures in select genes/gene regions in unfractionated peripheral blood between cases and controls.

The distinct differences in DNAm signatures observed from CpGs outside regulatory promoter regions substantiates an unbiased genome-wide approach to fully characterize the contributions of DNAm on disease susceptibility and related endophenotypes.

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GWM Signatures Identified in CD19+B Cells

These data demonstrate clear separation of differentially methylated gene signatures in CD19+B cells among cases compared to unaffected controls.

Although the separation noted in CD4+ T cells between cases and controls is less striking, the variation of DNAm profiles in T cells in cases is notably greater, which may correlate with the variance in observed endophenotypes.
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