Defining the Immune Microenvironment in Myelodysplastic Syndrome and Acute Myeloid Leukemia Using Machine Learning

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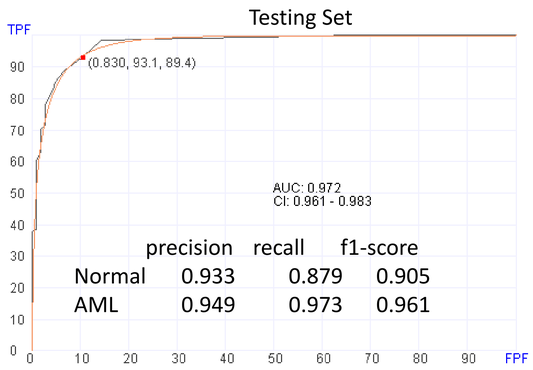
Introduction

lodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are caused by genetic and epigenetic abnormalities that overlap. Changes in the bone marrow (BM) microenvironment are believed to play a major role in the biology of MDS and AML.To study the bone marrow microenvironment (BME) in MDS and AML and to compare it with normal BME, we studied the expression profile of 43 immune biomarkers and evaluated the differences in the BME between AML and MDS and compared it to that of normal BME. These 43 immune biomarkers included B- and T-cell markers, cytokines and chemokines.

Methods and Materials

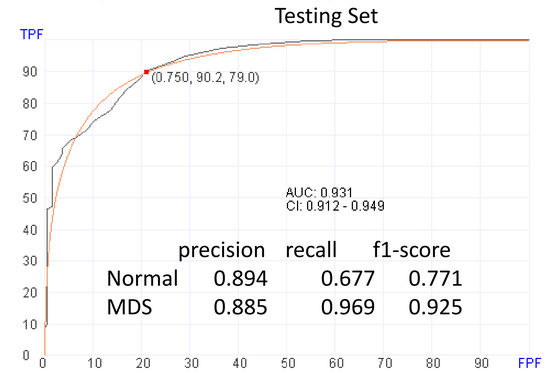
RNA was extracted from fresh bone marrow aspiration samples from 626 patients with AML, 564 patients with MDS, and 1449 individuals having bone marrow without any mutations or having low level mutations determined to be CHIP (clonal hematopoiesis of indeterminate potential) and considered normal. RNA levels of 42 immune biomarkers were quantified using next generation sequencing as a part of targeted RNA sequencing of 1408 genes. Using a machine learning algorithm, we first selected the relative genes that distinguish between two classes using two criteria: performance of each gene with K-fold cross-validation (K=12) and second based on stability measure using statistical significance tests. The selected genes were used to predict one class from the other using random forest classifier. Samples were divided to training set (67%) and testing set (33%) for each classification.

10 Immune biomarkers can distinguish between normal and AML bone marrow microenvironment (BME).
Training set: 1390; Testing Set : 684



Genes: CYFIP2(T-cell adhesion), IL1R1, CXCR4, IL8, IL21R, CD44, CD28, CD79A, and IL7R, and CD8A.

15 Immune biomarkers can distinguish between normal and MDS bone marrow microenvironment (BME).
Training set: 1349; Testing Set : 664



Genes: CYFIP2(T-cell adhesion), CXCR4, IL1RAP, CD58, CD36, CD19, PAX5, CD79B, ID1, IL8, CD44, IL1R1, CD79A, IL21R, and CD74

Conclusions:

-Bone marrow microenvironment (BME) is significantly different in MDS and AML from normal.

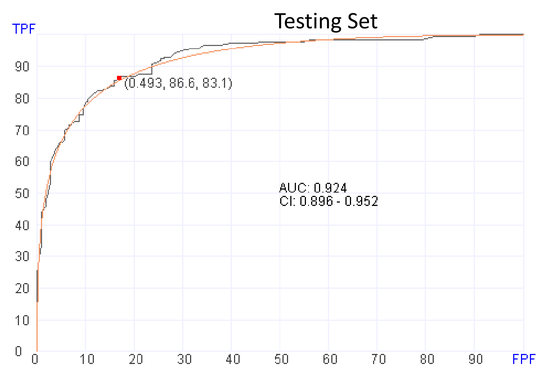
-10 to 15 immune biomarkers play major role in defining BME for each both AML and MDS with significant overlap.

-AML BME is specifically abnormal in CD28 and IL7R as compared with MDS.

-In general, reduction in the levels of these immune biomarkers is noted in MDS and AML as compared with normal marrow.

10 Immune biomarkers can distinguish between MDS and AML bone marrow microenvironment (BME).

Training set: 797; Testing Set : 392



Genes: IL1R1, CYFIP2(T-cell adhesion), CD44, IL1RAP, CXCR4, IL21R, CD74, IL8, CD28 and CD36.