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Original Article

Integrated analysis of genotype and phenotype reveals clonal evolution and cytogenetically driven disruption of myeloid cell maturation in myelodysplastic syndromes

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Abstract

Background

Myelodysplastic syndromes (MDS) are a heterogenous collection of clonal bone marrow diseases characterized by cytopenias, abnormal karyotypes, molecular abnormalities, and dysplasia by flow cytometry and/or morphology. The progression of MDS to severe cytopenias and/or overt leukemia is associated with the accumulation of additional cytogenetic abnormalities, suggesting clonal evolution. The impact of these accumulated abnormalities on myeloid maturation and the severity of the disease is poorly understood.

Methods

Bone marrow specimens from 16 patients with cytogenetic abnormalities were flow cytometrically sorted into three myeloid populations: progenitors, immature myeloid cells, and mature myeloid cells. Fluorescence in situ hybridization analysis was performed on each to determine the distribution of chromosomal abnormalities during myeloid maturation.

Results

Our findings revealed three distinct distributions of cytogenetic abnormalities across myeloid maturation, each of which corresponded to specific cytogenetic abnormalities. Group 1 had

continuous distribution across all maturational stages and contained patients with a single cytogenetic aberration associated with good-to-intermediate prognosis; Group 2 had accumulation of abnormalities in immature cells and contained patients with high-risk monosomy 7; and Group 3 had abnormalities defining the founding clone equally distributed across maturational stages while subclonal abnormalities were enriched in progenitor cells and contained patients with multiple, non-monosomy 7, abnormalities with evidence of clonal evolution.

Conclusions

Our findings demonstrate that low-risk abnormalities (e.g., del(20q) and trisomy 8) occurring in the founding clone display a markedly different disease etiology, with respect to myeloid maturation, than monosomy 7 or abnormalities acquired in subclones, which result in a disruption of myeloid cell maturation in MDS.