Associations of Genetic Variations in Altered Cellular Pathways in Haematopoietic and Mesenchymal Stem Cell Compartments in Myelodysplastic Syndromes

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Abstract

Myelodysplastic Syndromes (MDS) are clonal hematopoietic stem cell (HSCs) disorders. Mesenchymal stem cells (MSCs) of the bone marrow (BM) have implications in MDS pathogenesis. Functional deficiencies have been reported in both HSCs and MSCs derived from MDS.

To gain potential insights into the pathway abnormalities in MDS, we analyzed 54 genes related to major cellular mechanisms: epigenetic regulation, cohesion complex, cell division, transcription, splicisome machinery and signal transduction in HSCs and MSCs derived from BM of 20 *de novo* MDS patients. Next generation sequencing was used to identify genetic variations (GVs). To understand the relationships among mutational patterns, mutated genes were assessed for their co-occurrence. Fisher's exact test was performed on all gene pairs that showed overlapping pattern of GVs to identify significant gene associations and visualized in a Circos diagram.

The most frequently affected pathways in both cell types were epigenetic regulation (chromatin remodeling, DNA methylation) and transcription. In HSCs, *KDM6A* gene was co-mutated with *PHF6*, *DNMT3A*, *STAG2*, *ETV6*, *BCOR*/*BCORL1*, *RUNX1* and *SF3B1* ($p<0.05$). The most significant association was observed between *KDM6A* and *BCORL1* genes ($p= 0.0012$). Moreover, *DNMT3A* and *FBXW7*, *EZH2* and *PHF6*, *ETV6* and *STAG2* were shown to be co-mutated. In MSCs, GVs in the genes in the epigenetic mechanisms and cohesion complex were shown to be co-existing. The most significant association was observed between *TET2* and *RAD21* ($p= 0.0032$). Genes associated with the epigenetic regulation (*TET2* and *EZH2*, *EZH2* and *KMT2A*, *ATRX* and *BCOR)* were co-mutated in MDS-MSCs.

Altered cellular pathways may contribute to the underlying proliferative and differentiation deficiencies in HSCs and lack of haematopoietic supportive capacity of MSCs in MDS. Identification of the affected cellular pathways and gene associations in HSC and MSC compartments in MDS raise the

prospect of uncovering the underlying molecular mechanisms and potential new diagnostic and drug targets for MDS.

Keywords: Myelodysplastic syndromes, haematopoietic stem cells, mesenchymal stem cells, associations of genetic variations