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Acute Leukemias

ACUTE MYELOID LEUKEMIA-DERIVED EXTRACELLULAR VESICLES INDUCED DNA METHYLATION CHANGES RESPONSIBLE FOR INFLAMMATORY PROGRAM IN NORMAL HEMATOPOIETIC STEM PROGENITOR CELLS

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Acute Myeloid Leukemia (AML) cells communicate with surrounding normal cells, including hematopoietic stem progenitor cells (HSPCs), in the bone marrow, and modify their fate supporting tumor growth. This communication can be mediated by Extracellular Vesicles (EVs), small vectors carrying a range of tumor molecular information. One of the hallmarks of AML is the aberrant DNA methylation. It is not known if and how AML cells can modify the epigenomic profile of healthy HSPCs. Here, we investigated the DNA methylation profile of HSPCs after exposure to AML derived-EVs.

Cord blood derived-HSPCs were treated with AML cell line derived-EVs for 20 hours and then their DNA methylation profile was analyzed by methylation array. We cross-referenced differential methylated genes (dmGs) with differential expressed genes (deGs) obtained by gene expression profile of same EV treated-HSPCs. Gene ontology was performed on dmGs and deGs. To confirm the expression of some genes, digital PCR was applied.

AML-EVs induced DNA methylation changes in HSPCs after short time exposure, showing 110-890 dmGs. In particular, we reported a DNA hypo-methylation in both promoter and body regions. DmGs showed an enrichment in hematopoietic and immunological processes, inflammation, cell movement and AML pathways. The intersection between dmGs and deGs identified 20 common genes, including DSE, SEMA4A, NFKB1 and MTSS1, whose over-expression could be associated with the hypo-methylation of their gene body, and other ones, such as SLA and CUTA whose down-expression could be associated with the hypo-methylated promoter. These deGs were involved in NF-kB pathway, interleukin mediate Toll like receptor signaling and, of note, in tumor.

This study is the first proof-of-concept that AML-EVs were able to induce changes in DNA methylation of HSPCs modulating the expression of genes involved in inflammatory processes capable of modifying normal hematopoiesis towards leukemic like processes.