Epigenomic analysis reveals a specific DNA methylation program of metastasis-competent circulating tumor cells in colorectal cancer

Aida Bao-Caamano[1]
Nicolas Costa-Fraga[1], Laure Cayrefourcq[2], María Amalia Jácome[3], Aitor Rodriguez-Casanova[1], Laura Muinelo-Romay[4], Rafael López-López[4], Catherine Alix-Panabières[5] and Angel Diaz-Lagares[4]
[1] ONCOMET, Health Research Institute of Santiago (IDIS). Universidade de Santiago de Compostela (USC).
[2] Laboratory of Rare Human Circulating Cells, University Medical Center of Montpellier. CREEC, MIVEGEC, University of Montpellier, CNRS, IRD, Montpellier.
[3] MODES Group, CITIC, Universidade da Coruña
[4] ONCOMET, Health Research Institute of Santiago (IDIS). CIBERONC. Universidade de Santiago de Compostela (USC).
[5] Laboratory of Rare Human Circulating Cells, University Medical Center of Montpellier. CREEC, MIVEGEC, University of Montpellier, CNRS, IRD, Montpellier. European Liquid Biopsy Society (ELBS).

Background & objectives

Metastasis is the main cause of cancer-related deaths in patients with solid tumors, including colorectal cancer (CRC). Circulating tumor cells (CTCs) and epigenetic alterations are involved in the development of metastasis. The aim of this study was to characterize epigenomic properties based on DNA methylation of metastasis-competent CTCs in CRC.

Methods

The DNA methylome of the human colorectal cancer-derived cell line CTC-MCC-41 was compared with primary (HT29, Caco2, HCT116, RKO) and metastatic (SW620 and COLO205) CRC cells using a genome-wide methylation analysis with Infinium MethylationEPIC array. The association between the methylation and the transcriptional profile of CTC-MCC-41 was also evaluated. Differentially methylated CpGs were validated with pyrosequencing and qMSP.

Results

CTC-MCC-41 cells showed a globally methylation profile different to primary and metastatic CRC cells. This methylation pattern was characterized in CTC-MCC-41 by a slight predominance of hypomethylated CpGs mainly distributed in CpG-poor regions. Promoter CpG islands and shore regions of CTC-MCC-41 showed a specific methylation profile that was associated with its transcriptional status. This methylation portrait was associated with relevant

cancer pathways, mainly Wnt signaling. The promoter hypermethylation and hypomethylation of relevant genes in CTC-MCC-41 was also validated. Finally, the expression of epigenetically silenced genes was restored in CTC-MCC-41 cells after 5-aza-2'-deoxycytidine treatment.

Conclusion

This study provides new insights into the epigenomic landscape of metastasis-competent CTCs, revealing biological information for metastasis development, as well as new potential biomarkers and therapeutic targets of CTCs for colorectal cancer patients.