THE IMMUNOLOGICAL AND GENOMIC PROFILING OF COLORECTAL AND BREAST CANCER CELL LINES CAN DISTINGUISH STEM LIKE FROM DIFFERENTIATED TUMOR CELLS: IMPLICATIONS FOR CANCER IMMUNOTHERAPY

1Neha Gopinath, 2Tanwir Habib, 1Mohammed Toufiq, 1Alice Turdo, 1Asma Al-Sulaiti, 1Ishita Gupta, 1Rebecca Mathew, 1Harshitha Shobha Manjunath, 3Matilde Todaro, 3Giorgio Stassi, 4Sara Tomei, 3Silvano Femmos, 3Ira Skoroshtova, 1Cristina Macalli, 1Sidra Medicine, Doha, Qatar; 2Weill Cornell Medicine, Doha, Qatar; 3University of Palermo, Palermo, Italy; 4MGH, Pittsburgh, PA, USA; 5University of Innsbruck, Innsbruck, Austria

Background Rare cells endowed with “stemness” and tumor initiating properties, cancer stem cells (CSCs), are considered responsible of metastatization and resistance to therapy, including immunotherapy. The aim of this study is to identify the molecular mechanisms regulating the immunological properties of CSCs isolated from solid tumors.

Methods CRC (N=15) and BC (N=21) cell lines, including differentiated tumor cells and CSCs, and, for BC cell lines, selected in vitro for radioresistance or invasiveness were used for this study. The expression of HLA molecules and the components involved in the antigen processing machinery (APM) was assessed through flow cytometry. DNA and RNA were isolated from these cell lines. The nCounter platform (Nanostring) was utilized to assess the hybridization with 800 probes for miRNAs and the RNA seq-based transcriptomic profile was also assessed. The methylation profiling of cancer cell lines was investigated through Infinium EPIC arrays (Illumina). In addition, the co-culture of tumor cells with HLA-matched lymphocytes, either with or without the treatment with immunomodulatory or epigenetic agents, was performed to assess the ability of the CRC and BC cells to elicit antigen-specific T cell responses.

Results A general impairment of the expression of HLA and APM (e.g., LMPs, TAP and tapasin) molecules was observed in CRC and BC lines. The down-modulation of the expression of HLA and APM was superior in “stem-like” cells as compared to the differentiated tumor cells. The treatment of these cells with immunomodulating or epigenetic agents could only partially restore the expression of these molecules. The induction in vitro of anti-tumor T cell responses through the co-culture of tumor cells with PBMCs, was suboptimal and with variability depending on the subtype of cells and the pre-treatment or not of tumor cells with either immunomodulating or epigenetic agents.

Differential miRNAs, transcriptomic and methylation profiles (p<0.05) were identified in either CRC or BC cells with stemness properties vs. differentiated cells, and in different subtypes of cells. These includes genes and their regulators involved in immunological functions.

The integration analyses among methylation, miRNAs and transcriptomic profiles is under investigations, although preliminary results are available showing the differential involvement in CSCs vs. differentiated tumor cells of immune related pathways.

Conclusions The immunological and genomic profiles of CRC and BC are associated with cell subtypes. These investigations will contribute to understand the mechanisms regulating the biological and immunological properties of tumor cell endowed with variable cell fate and their susceptibility to immunotherapy.

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Ethics Approval The study obtained ethics approval from both Sidra Medicine #1805024172, and Hamad Medical Corporation #MRC-03-17-150 institutional review boards; participants gave informed consent before taking part to the study.