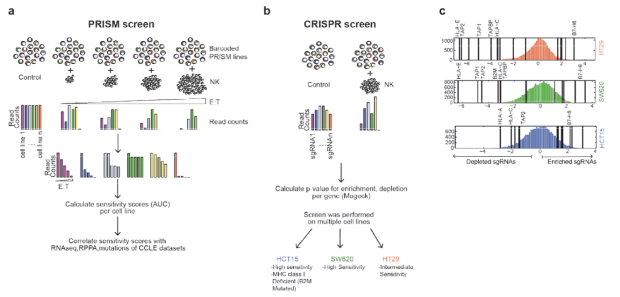

Abstract 36 Figure 1 Overview of PRISM and CRISPR studies a, Schematic depiction of PRISM study. b, Schematic depiction of CRISPR screens. c, Histogram of gene fold changes (z-scores). Listed are selected genes with most prominent p-values across more than one screen.

associated with resistance or sensitivity to NK cells. In addition, we applied genome-scale CRISPR-based gene editing screens in several solid tumor cell lines to interrogate, at a functional level, which genes regulate tumor cell response to NK cells.[3] [4]Figure 1 schematically depicts the two screens.

Results Based on these orthogonal studies, NK sensitive tumor cells tend to exhibit high levels of the NK cell-activating ligand B7-H6 (NCR3LG1); low levels of the inhibitory ligand HLA-E; microsatellite instability (MSI) status; high transcriptional signature for chromatin remodeling complexes and low antigen presentation machinery genes. Treatment with HDAC inhibitor reduced the sensitivity of SW620 colon cancer cells, increased antigen presentation machinery, including HLA-E, and reduced B7-H6. Importantly, transcriptional signatures of NK cell-sensitive tumor cells correlate with immune checkpoint inhibitor resistance in clinical samples. Widespread analysis of CCLE transcriptional signatures revealed that cell lines with mesenchymal-like program tend to be more sensitive to NK cells, compared with epithelial-like cell lines. Indeed, mesenchymal tumors tend to have lower expression of antigen presentation machinery in both CCLE and TCGA.

Conclusions This study provides a comprehensive map of mechanisms regulating tumor cell responses to NK cells, with implications for future biomarker-driven applications of NK cell immunotherapies. The integration of PRISM and CRISPR identified potential regulators of tumor cell response to NK cell, which upon further validation, may serve as biomarkers in future NK cell-based studies. Moreover, NK cells may complement T-cells, killing tumor cells that do not respond to immune checkpoint inhibitors.

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REFERENCES

1. Yu C, *et al*., High-throughput identification of genotype-specific cancer vulnerabilities in mixtures of barcoded tumor cell lines. *Nat Biotechnol* 2016. **34**(4): p. 419–23.
2. Ghandi M, *et al*. Next-generation characterization of the cancer cell line encyclopedia. *Nature* 2019. **569**(7757): p. 503–508.
3. Doench JG, *et al*. Optimized sgRNA design to maximize activity and minimize off-target effects of CRISPR-Cas9. *Nat Biotechnol* 2016. **34**(2): p. 184–191.
4. Shalem O, *et al*. Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science* 2014;**343**(6166): p. 84–87.

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37 MONITORING THE EVOLUTION OF INFLAMMATORY BOWEL DISEASE (IBD) IN PEDIATRIC AND ADULT COHORTS OF PATIENTS TO IDENTIFY BIOMARKERS TO PREDICT CANCER RISK

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Background Patients with inflammatory bowel disease (IBD) have increased risk of developing colorectal cancer (CRC), depending on the duration and severity of the disease. The evolutionary process in IBD is driven by chronic inflammation leading to epithelial-to-mesenchymal transition (EMT) events in colonic fibrotic areas. EMT plays a determinant role in tumor formation and progression, through the acquisition of 'stemness' properties and the generation of neoplastic cells. The aim of this study is to monitor EMT/cancer initiating tracts in IBD in association with the deep characterization of inflammation in order to assess the mechanisms of IBD severity and progression towards malignancy.

Methods 10 pediatric and 20 adult IBD patients, admitted at Sidra Medicine (SM) and Hamad Medical Corporation (HMC) respectively, have been enrolled in this study, from whom gut tissue biopsies (from both left and right side) were collected. Retrospectively collected tissues (N=10) from patients with malignancy and history of IBD were included in the study. DNA and RNA were extracted from fresh small size (2–4 mm in diameter) gut tissues using the BioMasher II (Kimble) and All Prep DNA/RNA kits (Qiagen). MicroRNA (miRNA; N=700) and gene expression (N=800) profiling have been performed (cCounter platform; Nanostring) as well as the methylation profiling microarray (Infinium Methylation Epic Bead Chip kit, Illumina) to interrogate up to 850,000 methylation sites across the genome.

Results Differential miRNA profile (N=27 miRNA; $p<0.05$) was found by the comparison of tissues from pediatric and adult patients. These miRNAs regulate: i. oxidative stress damage (e.g., miR 99b), ii. hypoxia induced autophagy; iii. genes associated with the susceptibility to IBD (ATG16L1, NOD2, IRGM), iv. immune responses, such as TH17 T cell subset (miR 29). N=6 miRNAs (miR135b, 10a196b, 125b, let7c, 375) linked with the regulation of Wnt/b-catenin, EM-transaction, autophagy, oxidative stress and play role also in cell proliferation and mobilization and colorectal cancer development were differentially expressed ($p<0.05$) in tissues from left and right sides of gut. Gene expression signature, including genes associated with inflammation, stemness and fibrosis, has also been performed for the IBD tissues mentioned above. Methylation sites at single nucleotide resolution have been analyzed.

Conclusions Although the results warrant further investigation, differential genomic profiling suggestive of altered pathways involved in oxidative stress, EMT, and of the possible stemness signature was found. The integration of data from multiple platforms will provide insights of the overall molecular determinants in IBD patients along with the evolution of the disease.

Ethics Approval This study was approved by Sidra Medicine and Hamad Medical Corporation Ethics Boards; approval number 180402817 and MRC-02-18-096, respectively.

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