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Letter to the Editor

Cancer Research

CD39 Expression Defines Cell Exhaustion in Tumor-Infiltrating CD8$^+$ T Cells—Letter

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With great interest we read the article "CD39 Expression Defines Cell Exhaustion in Tumor-Infiltrating CD8$^+$ T Cells" published by Canale and colleagues in *Cancer Research* (1). Previously, expression of CD39 has been described mainly for regulatory T cells (2) and the relevance of CD39 as a mechanism of immune escape in cancer was further highlighted by observation that CD39 is expressed on cancer cells (3). Because exhausted T cells, the target population of immune checkpoint inhibition, do not express high levels of CD39 (4), it might be a promising strategy to create a synergistic effect

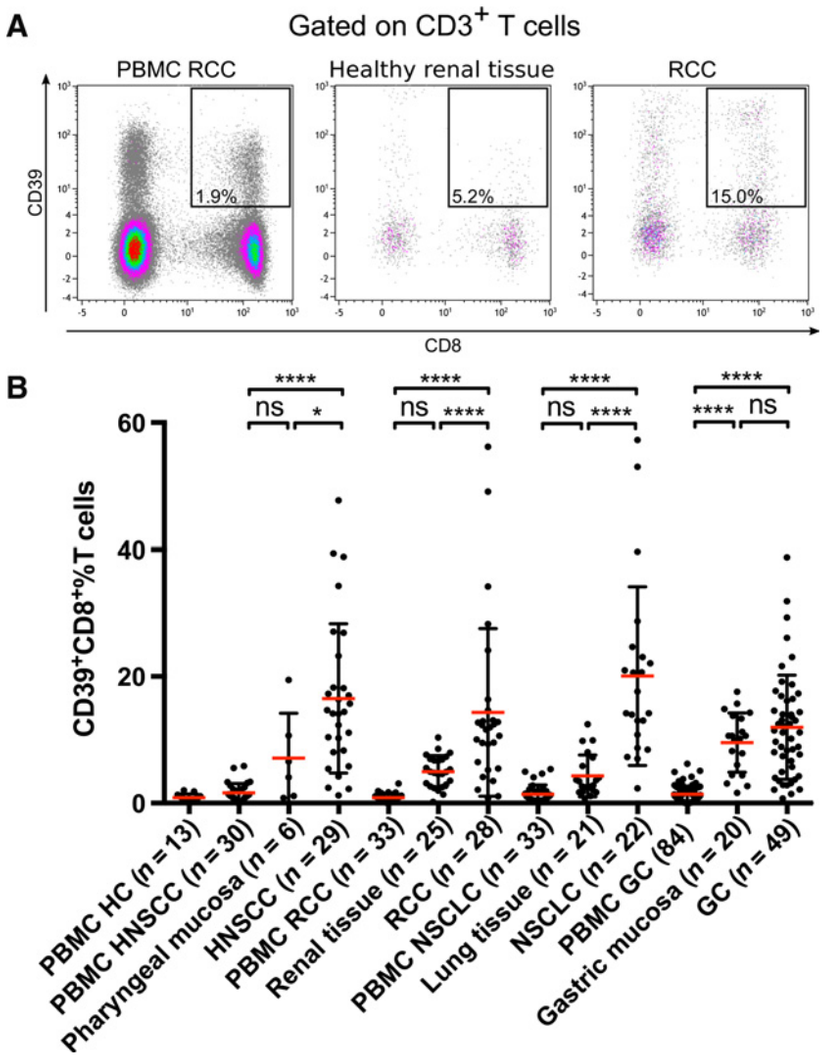

Figure 1.
CD39$^+$CD8$^+$ T cells are increased in tumor samples. PBMCs were isolated using density centrifugation. Tissue samples were mechanically and enzymatically digested using a gentleMACS dissociator with 320 U/mL Collagenase IV and 100 U/mL DNAse I for 1 hour at 37°C on a shaking incubator. Cells were freshly stained and analyzed (Gallios cytometer and Kaluza analysis software). Samples were gated for living cells (viability dye) and T cells (CD3$^+$CD45$^+$). **A,** Exemplary density plots of CD39$^+$CD8$^+$ T cells in PBMCs, healthy renal tissue, and tumor of one patient with renal cell carcinoma (RCC). **B,** Scatter plots showing results of flow cytometric analysis of CD8$^+$CD39$^+$ T cells in PBMC and single-cell suspensions of healthy tissue and tumor samples. HC, healthy controls. Means of lymphocytic subsets were compared using one-way ANOVA with Sidak multiple comparison test (Graphpad Prism 7). Data are presented as individuals with mean ± SD. ns, nonsignificant; *, $P \leq 0.05$; ****, $P \leq 0.0001$.

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between immune checkpoint inhibition and CD39 targeting, thereby improving efficacy of immune checkpoint inhibition in cancer.

The authors observed that a subset of $CD8^+$ T cells expresses the ATP-ecto-nucleotidase CD39 at similar levels as regulatory T cells. This $CD8^+CD39^+$ T-cell subset is enriched in tumor samples and almost absent in peripheral blood mononuclear cell (PBMC) or nonmetastatic tumor draining lymph nodes. Interestingly, enrichment of $CD8^+CD39^+$ T cells seems to be a common feature of preclinical tumor models (B16F10 and B16F10-OVA melanoma and MCA-OVA fibrosarcoma) as well as human melanoma and breast cancer. $CD8^+CD39^+$ T cells increased with tumor progression in the B16F10-OVA melanoma model. These cells were present in parental B16F10 melanoma, but the fraction was generally higher in highly immunogenic tumors expressing ovalbumin.

Although the presented study provides first evidence for a relevance of this cellular subset in human cancer, the data are limited to breast cancer and lymph node metastases of melanoma. We analyzed relevance of this highly interesting T-cell subset in four additional tumor entities. We could confirm presence of $CD8^+CD39^+$ T cells in head and neck squamous cell carcinoma, renal cell carcinoma, non–small cell lung cancer, and gastric adenocarcinoma (Fig. 1). In our opinion, the present study lacks a comparison with normal healthy tissue, which we provide in this letter. In accordance with data from PBMCs, $CD8^+CD39^+$ T cells were significantly decreased in healthy normal mucosa compared with three of the four tumor entities. Our own data further support relevance of this T-cell subset in four additional types of cancer and we demonstrate that this subset is highly specific for the tumor microenvironment regardless of the tumor origin. Taken together, the presented study and our data provide further translation evidence for clinical application of CD39 inhibition in basket trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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