Transcriptional Activity and Stability of CD39+CD103+CD8+ T Cells in Endometrial Cancer.

Abstract

Tumor-infiltrating CD8+ T cells (TIL) are of the utmost importance in anti-tumor immunity. CD103 defines tumor-resident memory T cells (T_RM cells) associated with improved survival and response to immune checkpoint blockade (ICB) across human tumors. Co-expression of CD39 and CD103 marks tumor-specific T_RM with enhanced cytolytic potential, suggesting that CD39+CD103+ T_RM could be a suitable biomarker for immunotherapy. However, little is known about the transcriptional activity of T_RM cells in situ. We analyzed CD39+CD103+ T_RM cells sorted from human high-grade endometrial cancers (n = 3) using mRNA sequencing. Cells remained untreated or were incubated with PMA/ionomycin (activation), actinomycin D (a platinum-like chemotherapeutic that inhibits transcription), or a combination of the two. Resting CD39+CD103+ T_RM cells were transcriptionally active and expressed a characteristic T_RM signature. Activated CD39+CD103+ T_RM cells differentially expressed PLEK, TWNK, and FOS, and cytokine genes IFNG, TNF, IL2, CSF2 (GM-CSF), and IL21. Findings were confirmed using qPCR and cytokine production was validated by flow cytometry of cytotoxic TIL. We studied transcript stability and found that PMA-responsive genes and mitochondrial genes were particularly stable.

In conclusion, CD39+CD103+ T_RM cells are transcriptionally active T_RM cells with a polyfunctional, reactivation-responsive repertoire. Secondly, we hypothesize that differential regulation of transcript stability potentiates rapid responses upon T_RM reactivation in tumors.

Introduction, brief summary and conclusions

The influence of tumor-infiltrating lymphocytes (TIL) on cancer prognosis is widely recognized, and TIL are studied in a wide variety of solid tumors. The composition of the immune infiltrate is of the utmost importance, as the immune architecture mainly determines whether the balance tips towards an anti-tumor or pro-tumor immune response [1]. CD103, the αE subunit of integrin αEβ7, defines intra-epithelial resident memory T cells (T_RM cells) with increased cytolytic potential, improved immune synapse formation, and increased tumor antigen sensitivity [2,3,4]. CD8+ T cells upregulate CD103 upon combined TCR stimulation and TGF-β signaling [5,6,7]. Even though TGF-β production is commonly attributed to dendritic cells and T regulatory cells, differentiated CD103+ T_RM are also capable of self-producing activated TGF-β1 to maintain CD103 expression on their cell surface [8]. CD103+ T_RM are associated with prolonged survival in many solid tumors [4,6,9,10,11,12,13], including endometrial cancer (EC). CD103+ T_RM, both in tumor and non-tumor tissue, are marked by expression of PDCD1, ITGAE, CXCR6, and SPRY1 in lung cancer [19]. Tumor-resident CD103+ T_RM expressed a unique genotype compared to non-tumor CD103+ T_RM, characterized by expression of ENTPD1 (CD39) [20]. Indeed, bystander, i.e., non-tumor specific T cells, lack CD39 expression [21]. CD39, also known as ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1), catalyzes the phosphohydrolysis of extracellular ATP and ADP to eventually synthesize immunosuppressive adenosine. CD39 is upregulated on activated T cells [22], regulates T cell activation and polarization, and is considered an immunosuppressive marker associated with T cell exhaustion [23,24]. CD39 has therefore been put forth as an immunoregulatory checkpoint and a new therapeutic target in cancer [25]. A further specification of T_RM cells in endometrial cancer might therefore be relevant, as CD39 and CD103 co-expression identifies tumor-resident, clonally expanded, tumor antigen-specific T cells with superior cytolytic capacity [19,20]. Moreover, tumor-resident CD103+ T_RM differentially express immune checkpoints such as CTLA4, TIM3, LAG3, and TIGIT, indicating T cell exhaustion due to excess antigen stimulation [9,18,19,26]. In line with this, CD103+ T_RM are linked to response to immune checkpoint blockade (ICB) [27,28]. Thus, it can be hypothesized that patients with both a sufficient number of T_RM cells and a specific subtype of T_RM cells are likely to respond to immunotherapy/immune checkpoint blockade. However, little is known about transcriptional activity of T_RM cells in situ.

We studied the transcriptional profile of high-grade endometrial cancer CD39+CD103+ T_RM cells in situ, after T cell
activation, and after transcriptional inhibition with actinomycin D in order to elucidate core elements necessary for successful T cell reactivation. Moreover, we studied the immune profile of TIL in the context of pretreatment with actinomycin D, a platinum-like chemotherapeutic. Resting CD39+CD103+ T<sub>R</sub> cells were transcriptionally active and expressed a characteristic tissue-resident transcriptional profile, including several immune checkpoints. Upon activation, T<sub>R</sub> cells upregulated markers of T cell activation, cytolytic activity, and cytokine production. Activated CD39+CD103+ T<sub>R</sub> cells differentially expressed PLEK, TWNK, and FOS, and cytokine genes IFNG, TNF, IL2, CSF2 (GM-CSF), and IL21. Secondly, we studied transcript stability and found that PMA-responsive immune genes and mitochondrial genes were particularly stable.

Taken together, our findings showed that CD39+CD103+ T<sub>R</sub> cells in high-grade endometrial cancer are polyfunctional T cells with a reactivation-responsive repertoire, despite their exhausted phenotype. Secondly, CD39+CD103+ T<sub>R</sub> showed increased transcript stability of PMA-responsive and mitochondrial genes, which may potentiate rapid responses upon T<sub>R</sub> cell reactivation in tumors. Thirdly, T<sub>R</sub> cells seem to incorporate activation-induced negative feedback mechanisms that halt T<sub>R</sub> activation, and targeting these may be of interest in optimizing response to immune checkpoint blockade.

**Keywords**

CD103; CD39; Endometrial cancer; Transcription; mRNA sequencing; T cells

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