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Fernando P Canale, Maria C Ramello, Nicolas Núñez, Cintia L Araujo Furlan, Sabrina N Bossio, Melisa Gorosito Serrán, Jimena Tosello Boari, Andrés Del Castillo, Marta Ledesma, Christine Sedlik, Eliane Piaggio, Adriana Gruppi, Eva V Acosta Rodríguez, Carolina L Montes (2017 Oct 26)
**CD39 expression defines cell exhaustion in tumor-infiltrating CD8+ T cells.**
*Cancer research*: [DOI: canres.2684.2016](http://example.com)

**Summary**

The ability of CD8+ T lymphocytes to eliminate tumors is limited by their ability to engender an immunosuppressive microenvironment. Here we describe a subset of tumor-infiltrating CD8+ T cells marked by high expression of the immunosuppressive ATP ecto-nucleotidase CD39. The frequency of CD39highCD8+ T cells increased with tumor growth but was absent in lymphoid organs. Tumor-infiltrating CD8+ T cells with high CD39 expression exhibited features of exhaustion, such as reduced production of TNF and IL-2 and expression of co-inhibitory receptors. Exhausted CD39highCD8+ T cells from mice hydrolyzed extracellular ATP, confirming that CD39 is enzymatically active. Furthermore, exhausted CD39highCD8+ T cells inhibited IFNγ production by responder CD8+ T cells. In specimens from breast cancer and melanoma patients, CD39highCD8+ T cells were present within tumors and invaded or metastatic lymph nodes, but were barely detectable within non-invaded lymph nodes and absent in peripheral blood. These cells exhibited an exhausted phenotype with impaired production of IFNγ, TNF, IL-2 and high expression of co-inhibitory receptors. Although T cell receptor engagement was sufficient to induce CD39 on human CD8+ T cells, exposure to IL-6 and IL-27 promoted CD39 expression on stimulated CD8+ T cells from human or murine sources. Our findings show how the tumor microenvironment drives the acquisition of CD39 as an immune regulatory molecule on CD8+ T cells, with implications for defining a biomarker of T cell dysfunction and a target for immunotherapeutic intervention.

Alice Barbarin, Emilie Cayssials, Florence Jacomet, Nicolas Gonzalo Nunez, Sara Basbous, Lucie Lefèvre, Myriam Abdallah, Nathalie Piccirilli, Benjamin Morin, Vincent Lavoue, Véronique Catros, Eliane Piaggio, André Herbelin, Jean-Marc Gombert (2017 Apr 12)
**Phenotype of NK-Like CD8(+) T Cells with Innate Features in Humans and Their Relevance in Cancer Diseases.**

**Summary**

Unconventional T cells are defined by their capacity to respond to signals other than the well-known complex of peptides and major histocompatibility complex proteins. Among the burgeoning family of unconventional T cells, innate-like CD8(+)- T cells in the mouse were discovered in the early 2000s. This subset of CD8(+) T cells bears a memory phenotype without having encountered a foreign antigen and can respond to innate-like IL-12 + IL-18 stimulation. Although the concept of innate memory CD8(+) T cells is now well established in mice, whether an equivalent memory NK-like T-cell population exists in humans remain
under debate. We recently reported that CD8(+) T cells responding to innate-like IL-12 + IL-18 stimulation and co-expressing the transcription factor Eomesodermin (Eomes) and KIR/NKG2A membrane receptors with a memory/EMRA phenotype may represent a new, functionally distinct innate T cell subset in humans. In this review, after a summary on the known innate CD8(+) T-cell features in the mouse, we propose Eomes together with KIR/NKG2A and CD49d as a signature to standardize the identification of this innate CD8(+) T-cell subset in humans. Next, we discuss IL-4 and IL-15 involvement in the generation of innate CD8(+) T cells and particularly its possible dependency on the promyelocytic leukemia zinc-finger factor expressing iNKT cells, an innate T cell subset well documented for its susceptibility to tumor immune subversion. After that, focusing on cancer diseases, we provide new insights into the potential role of these innate CD8(+) T cells in a physiopathological context in humans. Based on empirical data obtained in cases of chronic myeloid leukemia, a myeloproliferative syndrome controlled by the immune system, and in solid tumors, we observe both the possible contribution of innate CD8(+) T cells to cancer disease control and their susceptibility to tumor immune subversion. Finally, we note that during tumor progression, innate CD8(+) T lymphocytes could be controlled by immune checkpoints. This study significantly contributes to understanding of the role of NK-like CD8(+) T cells and raises the question of the possible involvement of an iNKT/innate CD8(+) T cell axis in cancer.

Thomas Simon, Julien Pogu, Séverine Rémy, Frédéric Brau, Sylvie Pogu, Maud Maquigneau, Jean-François Fonteneau, Nicolas Poirier, Bernard Vanhove, Gilles Blancho, Eliane Piaggio, Ignacio Anegon, Philippe Blancou (2017 Mar 27)

Inhibition of effector antigen-specific T cells by intradermal administration of heme oxygenase-1 inducers.


**Summary**

Developing protocols aimed at inhibiting effector T cells would be key for the treatment of T cell-dependent autoimmune diseases including type 1 autoimmune diabetes (T1D) and multiple sclerosis (MS). While heme oxygenase-1 (HO-1) inducers are clinically approved drugs for non-immune-related diseases, they do have immunosuppressive properties when administered systemically in rodents. Here we show that HO-1 inducers inhibit antigen-specific effector T cells when injected intradermally together with the T cell cognate antigens in mice. This phenomenon was observed in both a CD8(+) T cell-mediated model of T1D and in a CD4(+) T cell-dependent MS model. Intradermal injection of HO-1 inducers induced the recruitment of HO-1(+) monocyte-derived dendritic cell (MoDCs) exclusively to the lymph nodes (LN) draining the site of intradermal injection. After encountering HO-1(+)MoDCs, effector T-cells exhibited a lower velocity and a reduced ability to migrate towards chemokine gradients resulting in impaired accumulation to the inflamed organ. Intradermal co-injection of a clinically approved HO-1 inducer and a specific antigen to non-human primates also induced HO-1(+) MoDCs to accumulate in dermal draining LN and to suppress delayed-type hypersensitivity. Therefore, in both mice and non-human primates, HO-1 inducers delivered locally inhibited effector T-cells in an antigen-specific manner, paving the way for repositioning these drugs for the treatment of immune-mediated diseases.
Immunotherapy using checkpoint inhibitors has changed the way we treat several aggressive cancers such as melanoma, non-small cell lung and head & neck cancers, among others, with durable responses achieved in the metastatic setting. However, unfortunately, the vast majority of patients do not respond to checkpoint inhibition therapy and a minority of patients, who do respond to treatment, develop secondary resistance and experience relapse by mechanisms still inadequately understood. Emerging evidence shows that alterations in multiple signaling pathways are involved in primary and/or secondary resistance to checkpoint inhibition. In this review we discuss how selected cancer-cell autonomous cues may influence the outcome of cancer immunotherapy, particularly immune checkpoint inhibition.