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Human CD8⁺ T_{EMRA} cells in neurodegeneration: Foes and friends

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Human CD8⁺ effector memory T cells (T_{EM}) were first described over three decades ago [1] and have since been the focus of extensive research by numerous groups. There is now a general consensus that human CD8⁺ T_{EM} cells display phenotypic and functional features reflecting a history of repeated cell division, differentiation, and acquisition of effector functions [2]. Most studies have focused on individuals suffering from chronic inflammatory conditions, including cancer, autoimmune disorders, and, notably, viral infections such as HIV, EBV, and HCMV [3]. Further investigations revealed that circulating CD8⁺ T_{EM} cells can be induced not only by persistent antigen stimulation through the T cell receptor but also by environmental factors that provide survival cues, such as cytokines and other factors [4, 5]. Collectively, these studies contributed to the development of the concepts of *memory inflation*, *immunosenescence*, and *exhaustion* [6, 7].

From a functional standpoint, CD8⁺ T_{EM} cells were initially regarded as primarily cytotoxic—a reasonable assumption in the context of viral infection and tumor surveillance. However, subsequent research demonstrated that CD8⁺ T_{EM} cells comprise a heterogeneous population with diverse, and sometimes opposing, functions. In addition to cytotoxic cells, the CD8⁺ T_{EM} pool includes subsets with inflammatory, regulatory, and tissue-repair capabilities [3]. Despite this growing body of information, progress in defining specific functions of CD8⁺ T_{EM} subsets has been hampered by the absence of reliable molecular markers that distinguish the various subpopulations within this complex pool.

Among the many surface receptors described, CD45RA deserves particular attention. Initially characterized as a tyrosine phosphatase that regulates the phosphorylation state of the tyrosine kinase Lck in T cells, CD45RA expression changes dynamically during CD8⁺ T cell differentiation—disappearing early and reappearing at later stages. CD8⁺CD45RA⁺ T cells are considered effector cells capable of secreting IFN-γ, TNF-α, perforin, and granzymes, consistent with a cytotoxic profile [1]. In that regard, a key observation that had long been overlooked emerged recently. Thus, a recent study showed that among CD8⁺CD45RA⁺ T cells (CD8⁺ T_{EMRA}), two distinct subsets can be consistently identified: one expressing high levels of CD45RA (T_{EMRA}^{high}) and another expressing low levels (T_{EMRA}^{low}) [8]. Interestingly, the pattern of CD45RA expression parallels that of the CD8β chain of the CD8αβ receptor, suggesting interdependent regulation of these molecules [8]. The physiological relevance of this finding became evident in a cross-sectional study of elderly volunteers with differing cognitive status. Elderly individuals without cognitive decline exhibited significantly higher percentages of CD45RA^{low} and CD8β^{low} CD8⁺ T cells in peripheral blood compared to those with mild or severe cognitive decline [8]. Afterwards, it was demonstrated that CD8β^{low} T cells can be induced *in vitro* by IL-15, suggesting that their emergence in older individuals *in vivo* may result from combined antigenic and cytokine-driven activation [9].

Additional studies in the same cohort demonstrated that specific HLA class I serotypes—namely HLA-A23 and HLA-A24, which can serve as ligands for the killer-cell immunoglobulin-like receptor KIR3DL1—and the presence of dementia are associated with elevated plasma levels of soluble HLA class I molecules, highlighting an immunogenetic link between HLA variation and neurodegeneration [10]. Notably, certain KIR3DL1 alleles have been associated with protection from Parkinson's disease (PD) symptoms, implying that KIR3DL1-expressing cells may play a role in slowing PD progression [11]. Taken together, these findings suggest that increased levels of soluble HLA class I molecules in the plasma of cognitively impaired HLA-A23⁺ and HLA-A24⁺ elderly subjects could represent part of the immunomodulatory mechanisms triggered by ongoing neurodegeneration [10]. Overall, these results provide emerging evidence that adaptive immune cells—particularly CD8⁺ T lymphocytes—exert regulatory and trophic influences on the central nervous system. The identification of CD45RA, CD8β, and IFN-γ as potential immune correlates of cognitive performance

suggests that peripheral CD8⁺ T cell phenotypes may both reflect and influence neural integrity and cognitive function. We hypothesize that specific CD8⁺ T cell signatures in the elderly, defined by activation and memory markers along with cytokine profiles, are associated with preserved cognition and may exert protective or regenerative roles in the aging brain.

For decades, CD8⁺ T cells were viewed almost exclusively as the "soldiers" of the immune system, programmed to eliminate virally infected, neoplastic, or even neuronal cells [12, 13]. However, it is now evident that their role extends beyond defense: they also contribute to neuroregeneration and fine-tuning of brain homeostasis [3, 14, 15]. Indeed, subsets of activated human CD8⁺ T cells produce amphiregulin, an epidermal growth factor receptor (EGFR) ligand that enhances epithelial regeneration [16]. Moreover, in a mouse model, resolution of chemotherapy-induced peripheral neuropathy depended on CD8⁺ T cell–derived IL-13, which promoted macrophage IL-10 secretion and thereby facilitated recovery from neuropathic pain [17].

In summary, the adaptive immune system in general—and CD8⁺ T_{EMRA} cells in particular—represent not only a fighting force but also a maintenance and repair mechanism. There is a certain poetry in that duality: the same CD8⁺ T_{EMRA} cell capable of destruction is equally capable of reparation. In brain function and homeostasis, human CD8⁺ T_{EMRA} cells can thus be both foes and friends—two faces of the same coin (Figure 1).

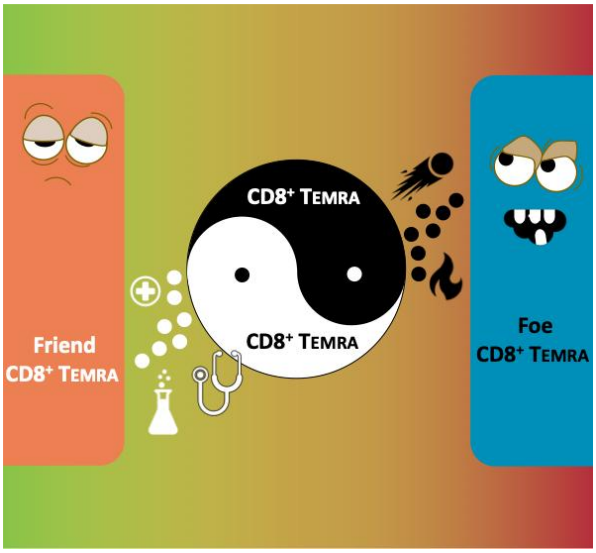

Figure 1 Cartoon illustrating the dual role (foe and friend) of human CD8⁺ T_{EMRA} cells within peripheral tissues. Adapted from ref. [18].

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Fernando A. Arosa (FAA) wrote the manuscript. Elsa M. Cardoso (EMC) reviewed the manuscript and designed Figure 1.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Hamann D, Baars PA, Rep MH, Hooibrink B, Kerkhof-Garde SR, Klein MR, et al. Phenotypic and functional separation of memory and effector human CD8⁺ T cells. The Journal of experimental medicine. 1997;186(9):1407-1418.
2. Muroyama Y, Wherry EJ. Memory T-cell heterogeneity and terminology. Cold Spring Harbor Perspectives in Biology. 2021;13(10):a037929.
3. Arosa FA, Esgalhado AJ, Padrão CA, Cardoso EM. Divide, conquer, and sense: CD8⁺ CD28⁻ T cells in perspective. Frontiers in Immunology. 2017;7:665.
4. Correia MP, Costa AV, Uhrberg M, Cardoso EM, Arosa FA. IL-15 induces CD8⁺ T cells to acquire functional NK receptors capable of modulating cytotoxicity and cytokine secretion. Immunobiology. 2011;216(5):604-612.
5. Li Y, Xiao J, Li C, Yang M. Memory inflation: Beyond the acute phase of viral infection. Cell Proliferation. 2024;57(12):e13705.
6. Sun Q, Dong C. Regulators of CD8⁺ T cell exhaustion. Nature Reviews Immunology. 2025:1-23.
7. Wu H, Prados MC, Vaeth M. Metabolic regulation of T cell exhaustion. Immune Discovery. 2025;1(1):10005.
8. Esgalhado AJ, Reste-Ferreira D, Albino SE, Sousa A, Amaral AP, Martinho A, et al. CD45RA, CD8β, and IFNγ Are Potential Immune Biomarkers of Human Cognitive Function. Frontiers in Immunology. 2020;11:592656.
9. Esgalhado AJ, Reste-Ferreira D, Weinhold S, Uhrberg M, Cardoso EM, Arosa FA. In vitro IL-15-activated human naïve CD8⁺ T cells down-modulate the CD8β chain and become CD8αα T cells. Frontiers in Immunology. 2024;15:1252439.
10. Cardoso EM, Lourenço-Gomes V, Esgalhado AJ, Reste-Ferreira D, Oliveira N, Amaral AS, et al. HLA-A23/HLA-A24 serotypes and dementia interaction in the elderly: Association with increased soluble HLA class I molecules in plasma. HLA. 2023;102(6):660-670.
11. Anderson KM, Augusto DG, Dandekar R, Shams H, Zhao C, Yusufali T, et al. Killer cell immunoglobulin-like receptor variants are associated with protection from symptoms associated with more severe course in Parkinson disease. The Journal of Immunology. 2020;205(5):1323-1330.
12. Zhang N, Bevan MJ. CD8⁺ T cells: foot soldiers of the immune system. Immunity. 2011;35(2):161-168.
13. Zhang Z, Duan Z, Cui Y. CD8⁺ T cells in brain injury and neurodegeneration. Frontiers in Cellular Neuroscience. 2023;17:1281763.
14. Hu D, Weiner HL. Unraveling the dual nature of brain CD8⁺ T cells in Alzheimer's disease. Molecular Neurodegeneration. 2024;19(1):16.

15. Latour YL, McGavern DB. Beneficial role of GZMK^{+}CD8^{+} T cells in neuro degeneration. Nature Immunology. 2025;26:1002-1003.
16. Delacher M, Schmidleithner L, Simon M, Stüve P, Sanderink L, Hotz-Wagenblatt A, et al. The effector program of human CD8 T cells supports tissue remodeling. Journal of Experimental Medicine. 2024;221(2):e20230488.
17. Singh SK, Krukowski K, Laumet GO, Weis D, Alexander JF, Heijnen CJ, et al. CD8^{+} T cell–derived IL-13 increases macrophage IL-10 to resolve neuropathic pain. JCI insight. 2022;7(5):e154194.
18. Arosa FA. On the Origin and Function of Human NK-like CD8^{+} T Cells: Charting New Territories: Frontiers Media SA; 2018.