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## **CD161 intermediate expression defines a novel activated, inflammatory and pathogenic subset of CD8+ T cells involved in multiple sclerosis**

B. Nicol, M. Salou, I. Vogel, A. Garcia, E. Dugast, J. Morille, Stéphanie Kilens, E. Charpentier, A. Donnant, S. Nedellec, et al.

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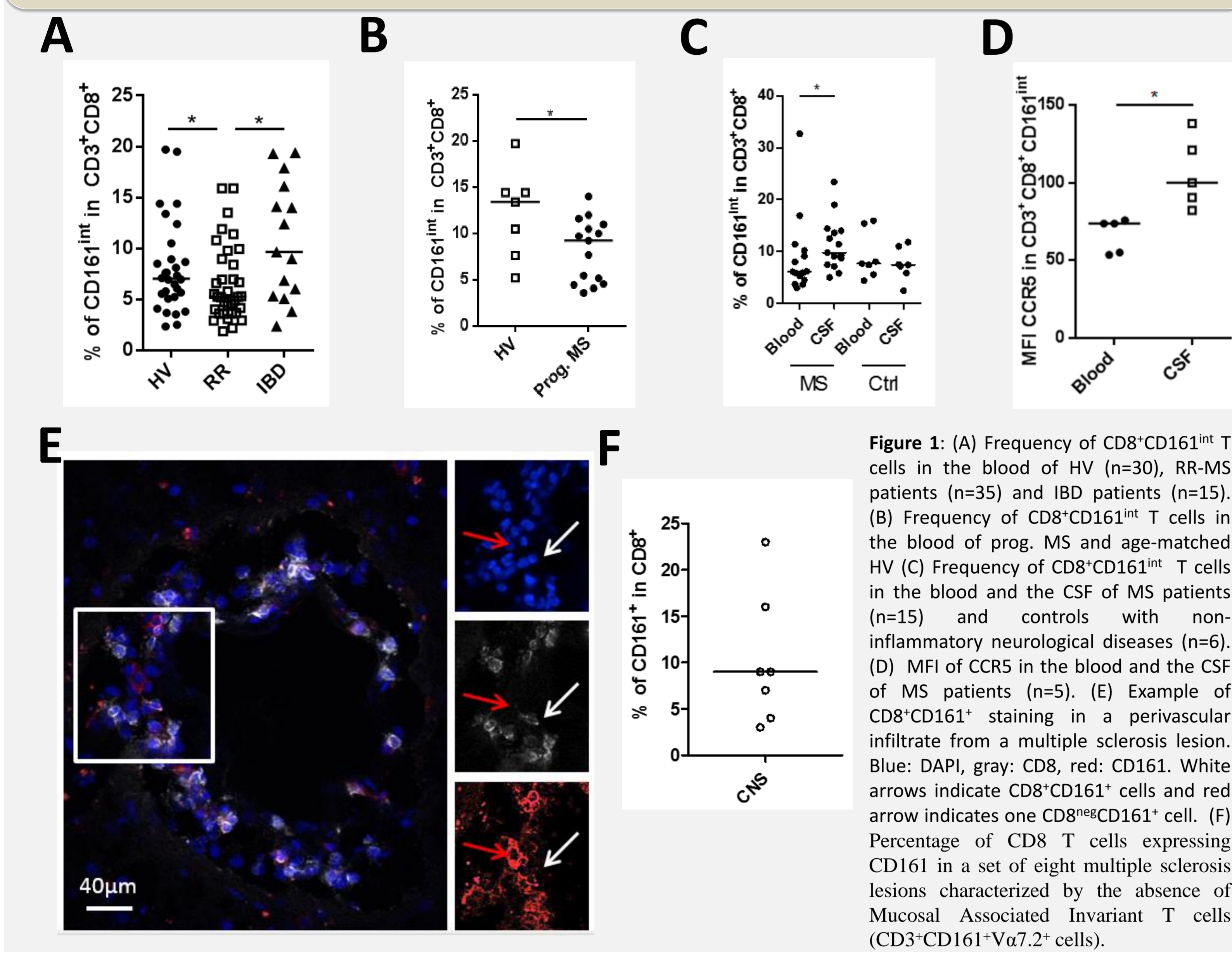
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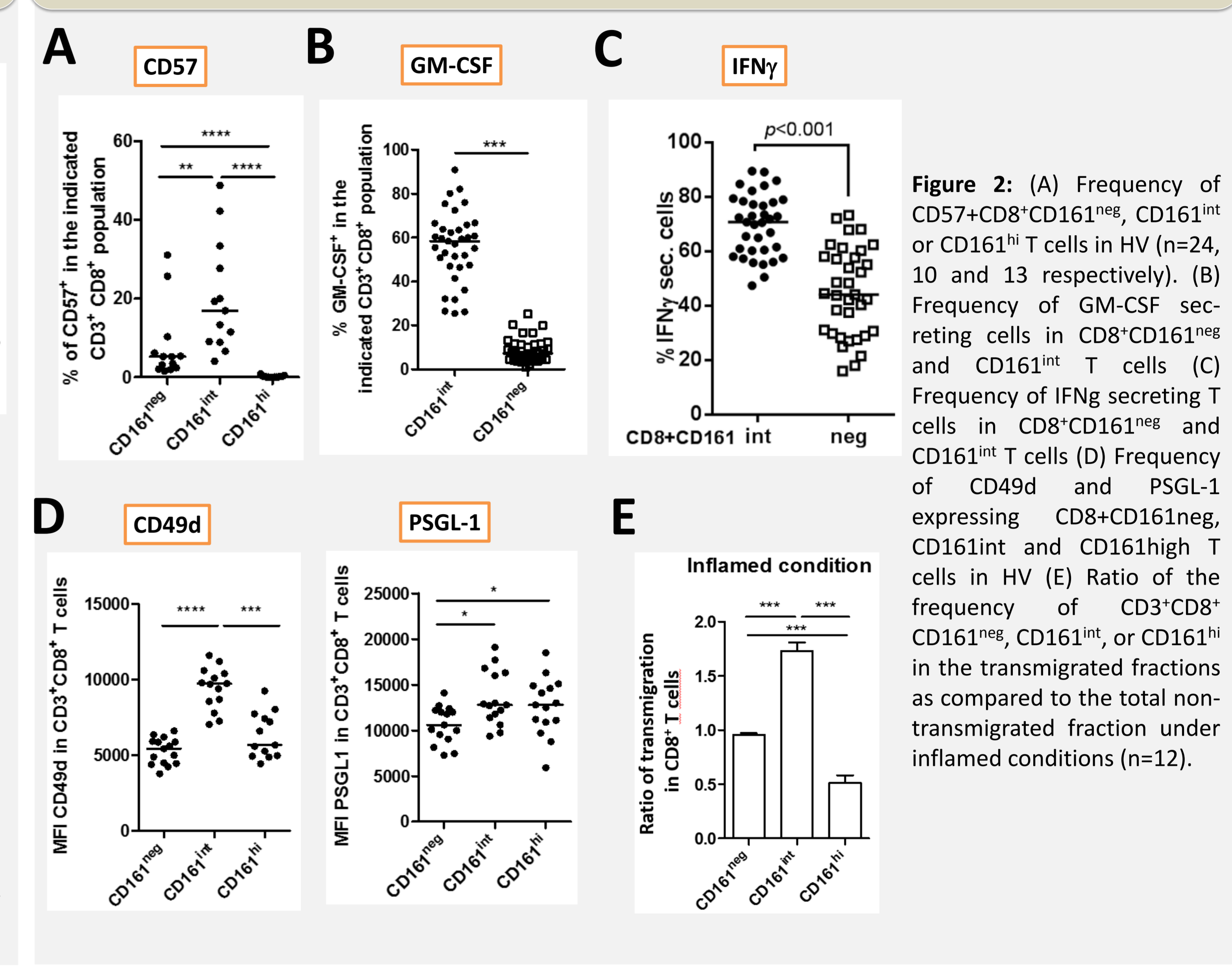
**Objective:** CD8 T cells are the most numerous infiltrating T cells in central nervous system (CNS) lesions of multiple sclerosis (MS) and several lines of evidence support their role in tissue damage. However, to date the precise phenotype of the circulating CD8 T cells that may be recruited from the periphery to invade the CNS remains largely undefined. It has been suggested that Tc17 lymphocytes may be involved and in humans, these cells are characterized by the expression of CD161. Whereas CD8<sup>+</sup> T cells with a high CD161 expression, representing mainly Mucosal Associated Invariant T cells, are likely not involved in the disease process, CD8<sup>+</sup> T cells with CD161 intermediate expression constitute a unique, recently described subset of CD8<sup>+</sup> T cells. Yet, its role in neuro-inflammation has not been investigated.

**Methods.** CD8<sup>+</sup>CD161<sup>int</sup> T cells from the blood of sex- and age-matched Relapsing Remitting (RR) untreated MS patients (n=35) and Healthy Volunteers (HV, n=30) were compared by flow cytometry (for frequency and phenotype). Their frequency and phenotype were also compared between the blood and the cerebrospinal fluid (CSF) in MS patients. Their transcriptional profile was analyzed by Fluidigm technology using Biomark™ HD (n=4 for HV and n=7 for MS). Their ability to transigrate through an *in vitro* blood-brain barrier (hCMEC/D3 cell line) have been studied and their presence and phenotype in CNS lesions were also studied by immunofluorescence staining on post-mortem CNS samples. Their *in vivo* behavior has been studied in an Graft-Versus-Host Disease (GVHD) model using NOD-*scid* gamma (NSG) mice.

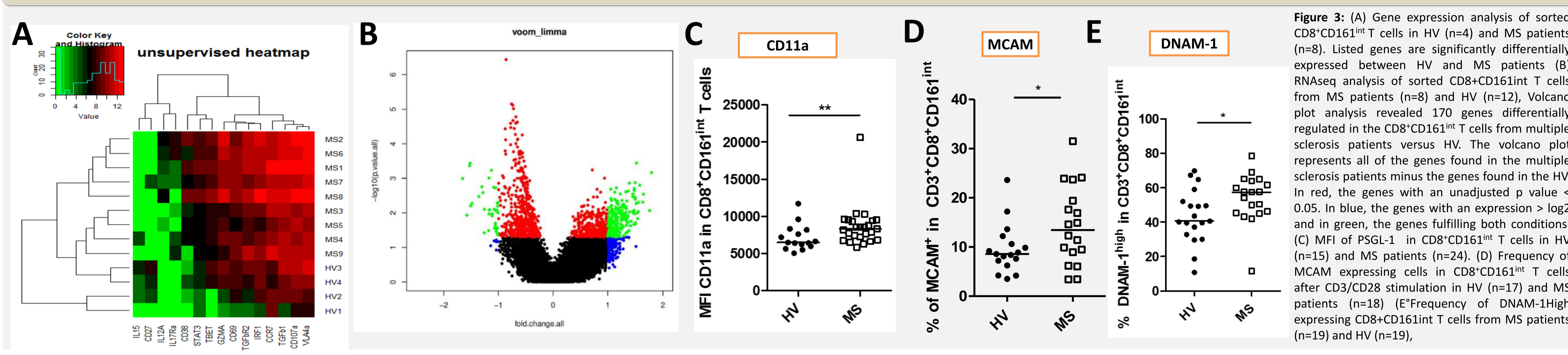
**The frequency of CD8<sup>+</sup>CD161<sup>int</sup> T cells is decreased in the blood and enriched in the CSF and CNS of MS patients**



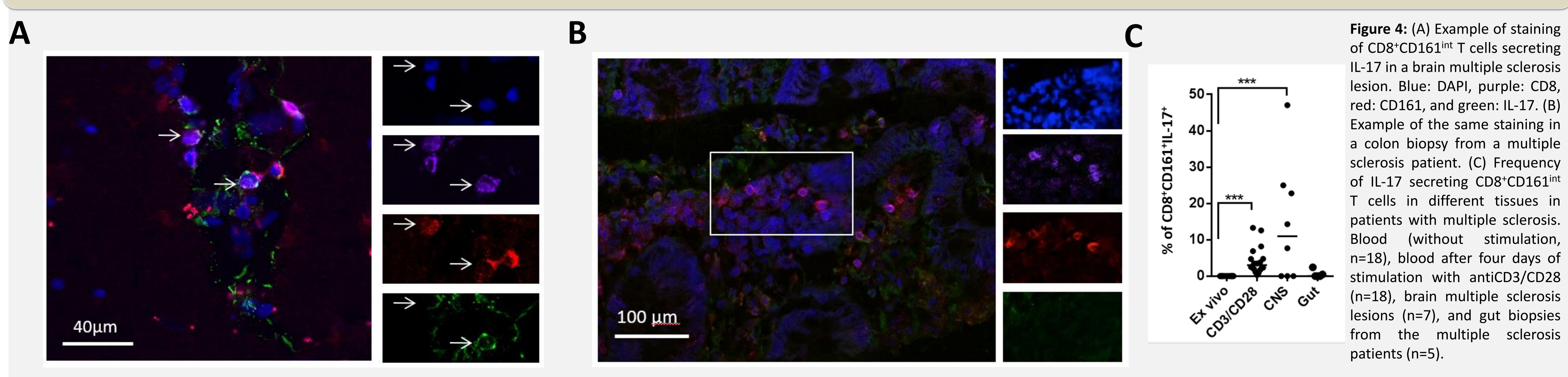
**CD8<sup>+</sup>CD161<sup>int</sup> T cells display a specific and activated phenotype with homing properties**



**CD8<sup>+</sup>CD161<sup>int</sup> T cells display transcriptomic and phenotypic alterations in the blood of MS patients**



**CD8<sup>+</sup>CD161<sup>int</sup> T cells are present and able to produce IL-17 in the CNS of MS patients**



**Conclusions:** We report here that CD8<sup>+</sup>CD161<sup>int</sup> T cells present characteristics of effector cells, up-regulate cell-adhesion molecules and have an increased ability to cross the blood-brain barrier and to secrete IFNγ and GM-CSF (and also IL-17 and IL-22, not shown). We further demonstrate that these cells are recruited and enriched in the CNS of MS subjects where they locally and specifically secrete IL-17. In the peripheral blood, RNAseq, RT-PCR and flow cytometry confirmed an increased effector and transmigration pattern of these cells in MS patients compared to healthy controls. Our data demonstrate that intermediate levels of CD161 expression identifies activated and effector CD8<sup>+</sup> T cells with pathogenic properties that are recruited to MS lesions. This suggests that CD161 may represent a biomarker and a valid target for the treatment of neuroinflammation.