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Alteration of CD8⁺CD45RC^{int/neg} regulatory T cells functions in Multiple Sclerosis and correlates with disease severity

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BACKGROUND

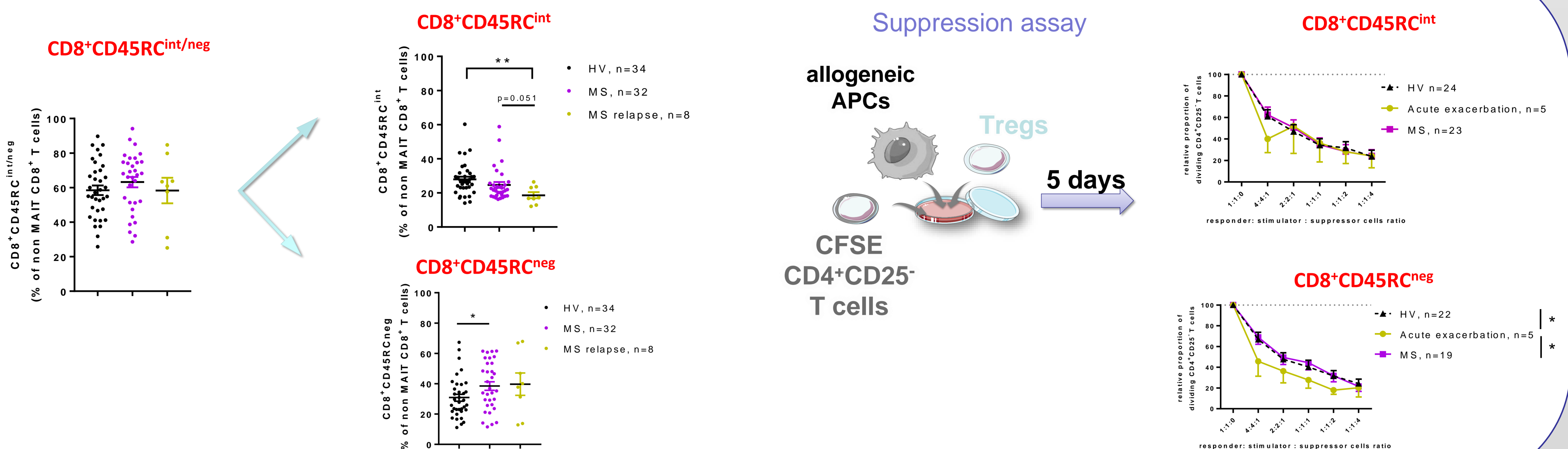
Autoimmune diseases can develop following pathological activation of autoreactive effector cells and/or, alternatively, after weakening of self-protective regulatory mechanisms. Most of the studies have focused on CD4⁺ Tregs and the **role of CD8⁺ Tregs in Multiple Sclerosis (MS) remains largely unexplored.** We previously reported the suppressive properties of rat and human CD8⁺CD45RC^{int/neg} Treg cells, expressing Foxp3 and acting through IFN γ , TGF β and IL34 cytokines (Guillonau, JCI, 2007; Bézie, JCI, 2015, Bézie, Front. Immunol., 2018). Thus, their **potency of suppression** make them strong candidates of disruptive immune tolerance, especially in MS where CD8⁺ T cells play a major role. **Thus, the overarching goal of this study is to define the role of CD8⁺ regulatory T cell in MS pathogenesis**

MATERIAL & METHODS

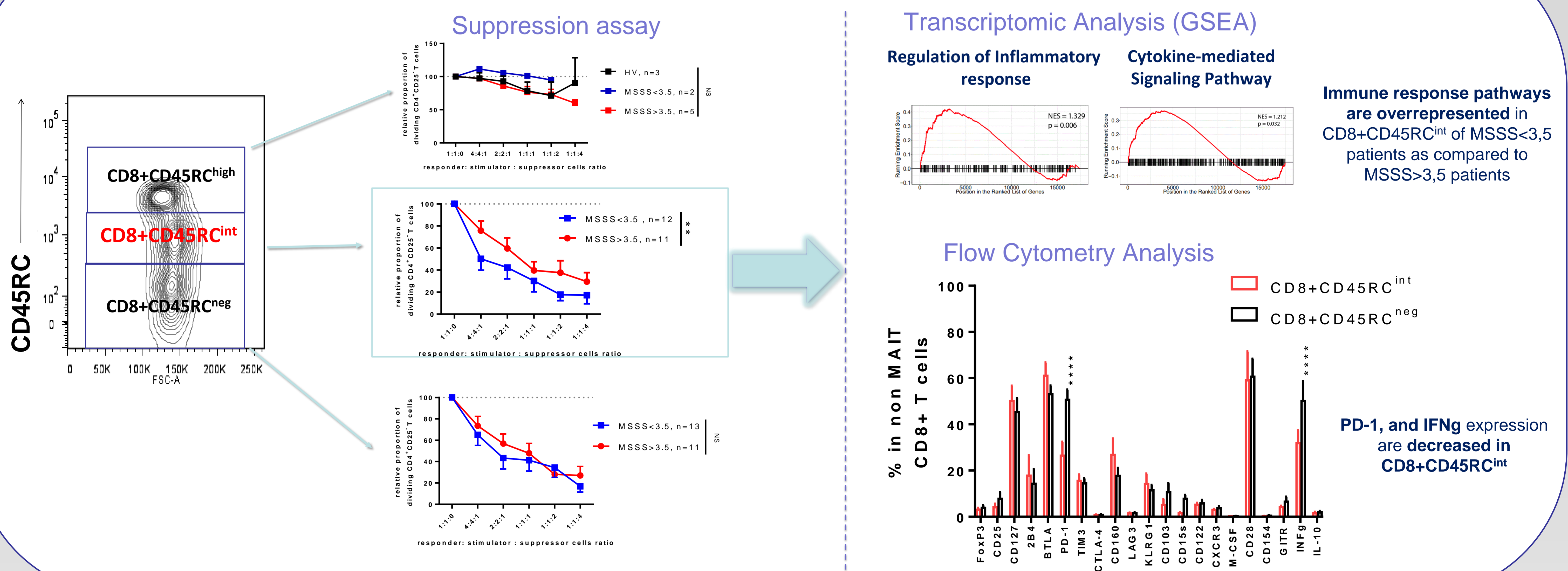
56 untreated relapsing-remitting MS patients and 52 age- and gender-matched healthy volunteers (HV) were recruited.

- **Tregs** were defined as CD3⁺CD8⁺ (or CD4⁻) CD161^{low}V α 7-CD45RC^{int/neg} T cells. MAIT cells were excluded from all analysis.
- **Staining:** T cells were stimulated or not 5h with PMA+ionomycin including 4h with BFA before FACS depending on the marker investigated.
- **Transcriptomic analysis:** 3'-Digital Gene Expression Sequencing was performed on unstimulated cells. Analysis was performed using R packages and KEGG, Reactome and Gene Ontology databases for Gene Set Enrichment Analysis (GSEA).

CD8⁺CD45RC^{int} TREGS FREQUENCY IN BLOOD IS REDUCED DURING EXACERBATION WHEREAS CD8⁺CD45RC^{neg} TREGS ARE MORE FREQUENT WITH ENHANCED SUPPRESSIVE FUNCTIONS



IN SEVERE PATIENTS WITH A HIGHER MULTIPLE SCLEROSIS SEVERITY SCORE, CD8⁺CD45RC^{int} TREGS FUNCTION IS IMPAIRED



CONCLUSION

For the first time, we demonstrate an **impairment of CD8⁺CD45RC^{int} Tregs in MS.**

We propose to define two populations of CD8⁺CD45RC Tregs:

- **CD8⁺CD45RC^{int} are dysfunctional in severe MS patients and less frequent during exacerbations**
- **CD8⁺CD45RC^{neg} Tregs react properly to inflammation with enhanced regulatory functions during exacerbations**

We suggest CD8⁺CD45RC^{int/neg} T cells and subsets may be potential therapeutic targets and prognostic tools in MS

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