Dual neutrophil subsets accelerate or brake inflammation in tuberculosis

Emilie Doz-Deblauwe, Badreddine Bounab, Florence Carreras, Julia Siveira Fahel, Sergio Oliveira, Mohamed Lamkanfi, Yves Le Vern, Pierre Germon, Julien Pichon, Christophe Paget, et al.

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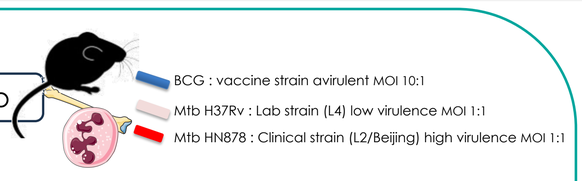
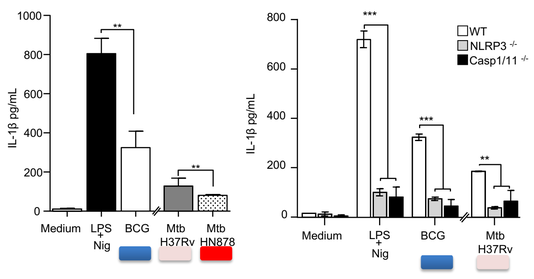
Neutrophils can be beneficial or deleterious during tuberculosis (TB). Based on the expression of MHC-II and programmed death ligand 1 (PD-L1), we distinguished two functionally and transcriptionally distinct neutrophil subsets in the lungs of mice infected with mycobacteria. Inflammatory [MHC-II-, PD-L1^{lo}] neutrophils produced inflammasome-dependent IL-1β in the lungs in response to virulent mycobacteria and "accelerated" deleterious inflammation, which was highly exacerbated in IFN-γR$^{-/-}$ mice. Regulatory [MHC-II+, PD-L1^{hi}] neutrophils "brake" inflammation by suppressing T-cell proliferation and IFN-γ production. Such beneficial regulation, which depends on PD-L1, is controlled by IFN-γR signaling in neutrophils. These findings add a layer of complexity to the roles played by neutrophils in TB and may explain the reactivation of this disease observed in cancer patients treated with anti-PD-L1.

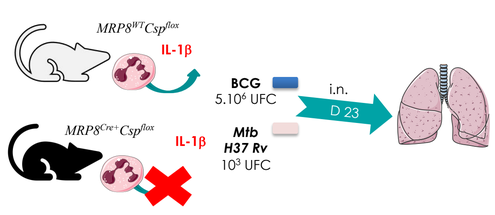
1- Two neutrophil subsets with two different functions

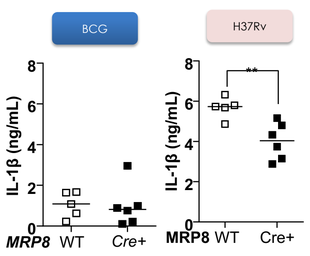
In vitro





In vivo





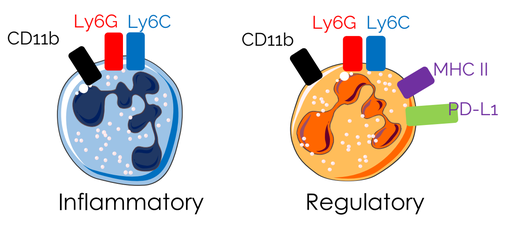
BCG: no difference

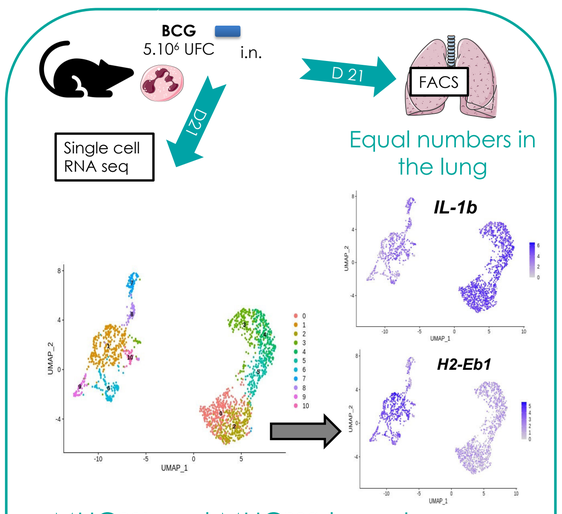
H37Rv: less IL-1β when neutrophils do not have inflammasome

Only virulent Mtb activates inflammasome *in vivo* in neutrophils

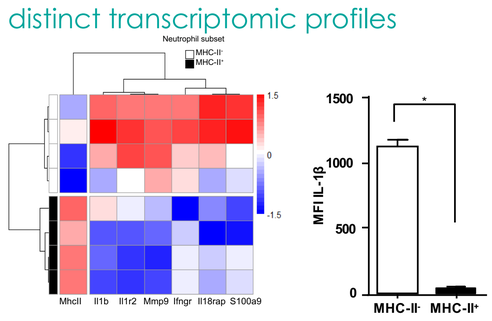
IL-1β

Neutrophils do contribute to IL-1β-driven inflammation in the lung

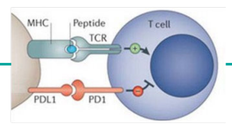


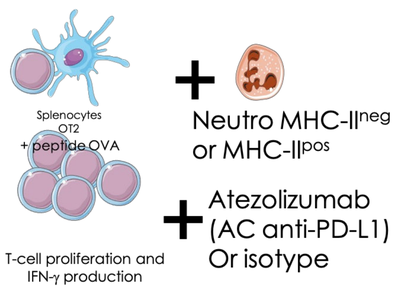


MHC^{pos} and MHC^{neg} have two distinct transcriptomic profiles



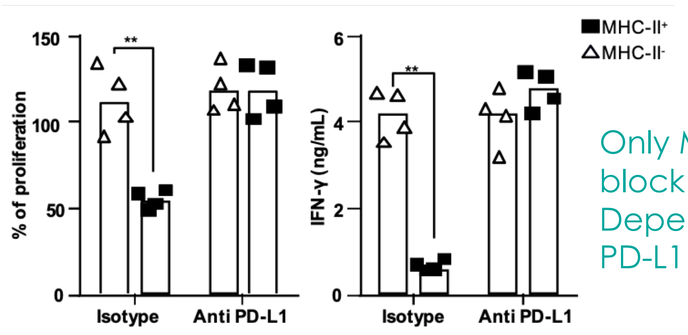
The MHC^{neg} subset is inflammatory & produces IL-1β





Neutro MHC-II^{neg} or MHC-II^{pos}

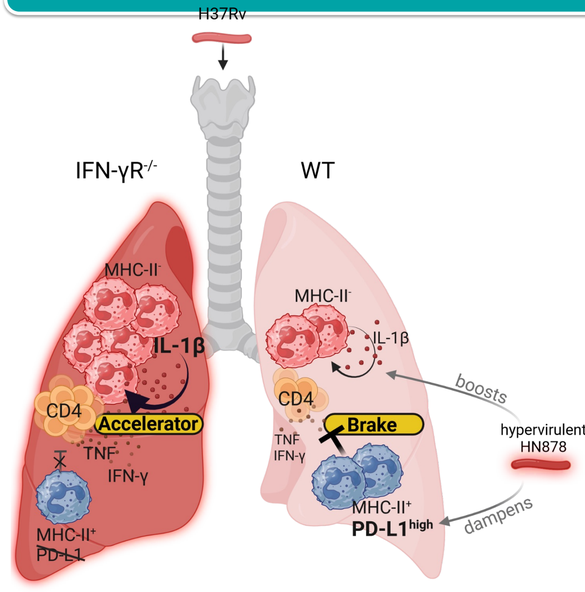
Atezolizumab (AC anti-PD-L1) Or isotype



Only MHC^{pos} block T-cells Depends on PD-L1

MHC-II^{neg} neutrophils produce IL-1β and are inflammatory, MHC-II^{pos}; PD-L1^{pos} neutrophils are regulatory

IN SUMMARY



Dual "brake" and "accelerator' functions exerted by the two neutrophil subsets on Mtb infection in the lung. Two functionally distinct neutrophil subsets are recruited to the lungs in response to mycobacterial infection. Classic [MHC-II^{-}, PD-L1^{lo}] neutrophils produce high levels of inflammasome-dependent IL-1β in the lungs in response to virulent mycobacteria and act as an "accelerator" of deleterious inflammation, which is highly exacerbated in IFN-γR$^{-/-}$ mice. Conversely, regulatory [MHC-II^{+}, PD-L1^{hi}] neutrophils act as a "brake" of inflammation by suppressing T-cell proliferation and IFN-γ production. This regulation depends on PD-L1 surface expression, controlled by IFN-γR signaling in neutrophils.

Many thanks to

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Valérie Quesniaux (INEM, UMR7355 CNRS, Université d'Orléans, France) *Aim2*$^{-/-}$, *Gsdmd*$^{-/-}$, *Nlrp3*$^{-/-}$, *Csp1/11*$^{-/-}$ mice,

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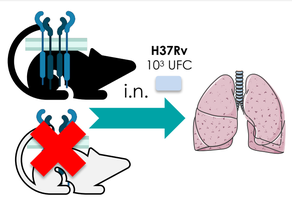
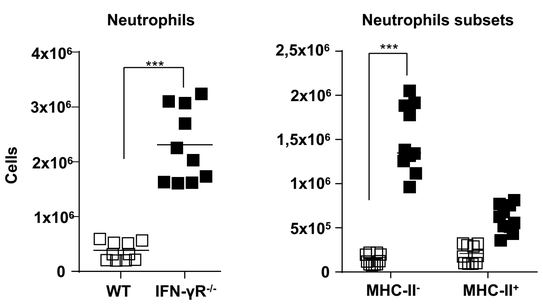
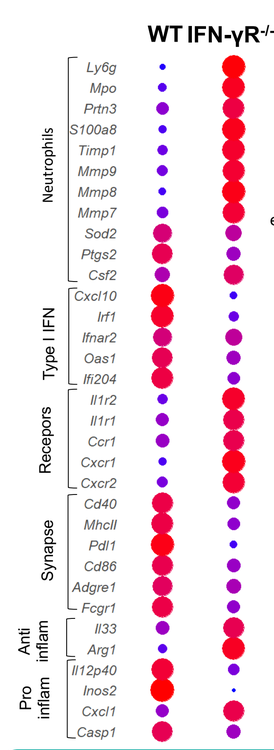
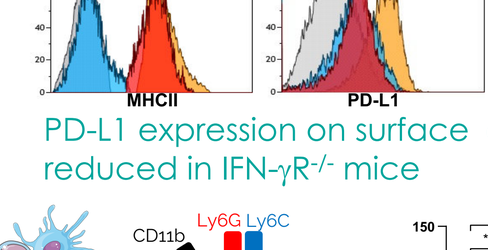
2- Is PD-L1 regulated by other signals ?

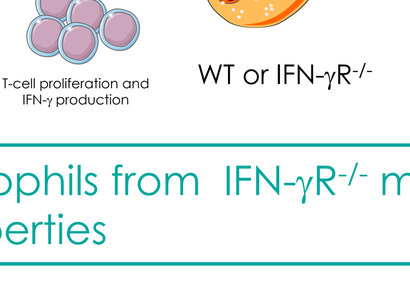


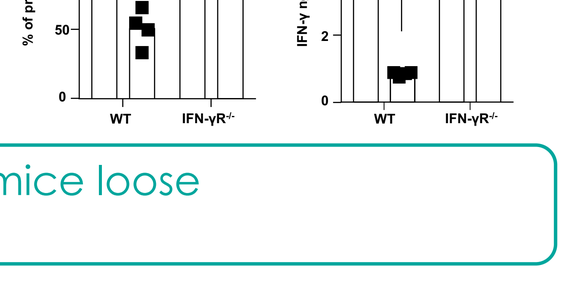






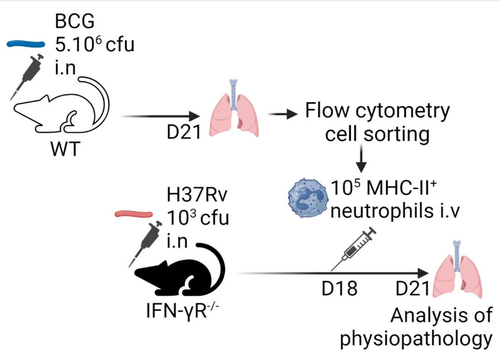
PD-L1 expression on surface of MHC-II^{pos} is dramatically reduced in IFN-γR$^{-/-}$ mice

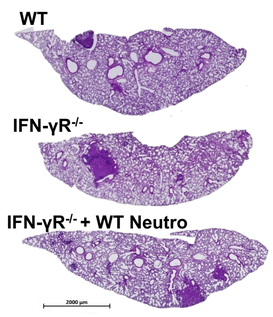


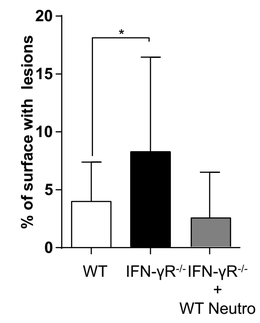


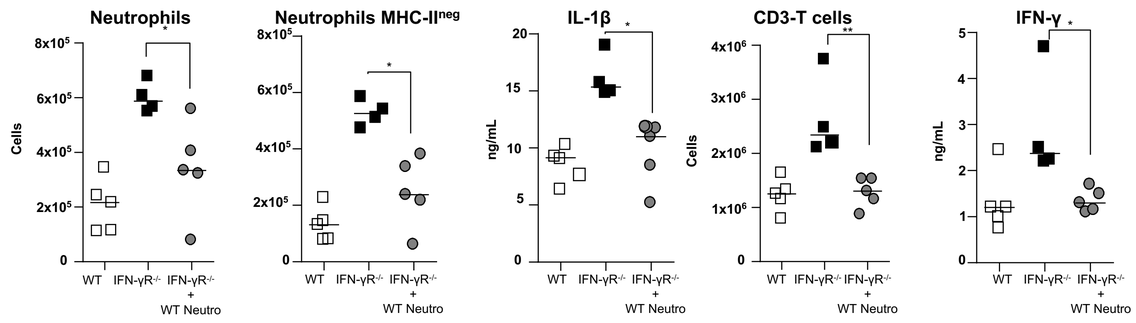
MHC-II^{pos} neutrophils from IFN-γR$^{-/-}$ mice loose regulatory properties

3- Can MHC-II^{pos} regulatory neutrophils dampen inflammation *in vivo*?









MHC-II^{pos} neutrophils from WT mice transferred into Mtb-infected IFN-γR$^{-/-}$ mice dampen lung inflammation.

Next....

- C3HeB/FeJ mice : distribution of regulatory and inflammatory neutrophils in a model with "proper TB granuloma" (see **poster by Doz-Deblauwe et al.**)
- Examine these two neutrophil subsets in TB patients
- Understand their respective roles in inflammatory compounds production in the lung during TB

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