Genetic and pharmacologic inhibition of TREM-1 limits the development of experimental atherosclerosis

Short title: TREM-1 inhibition reduces atherosclerosis

Jérémie JOFFRE **supervisor: Dr. H. Ait-Oufella**

INSERM U970 (Paris)

Background: Inflammation and innate immune responses activated through myeloid cells contribute to the initiation, progression and complications of atherosclerosis in experimental models. However, the critical upstream pathways that link innate immune activation to foam cell formation are still poorly identified.

Objectives: We hypothesized that activation of TREM (Triggering Receptor Expressed on Myeloid cells)-1 plays a determinant role in macrophage atherogenic responses.

Methods and Results: Ldlr-/- mice reconstituted with bone marrow deficient for Trem-1 (Trem-1-/-) showed a strong reduction of atherosclerotic plaque size in both the aortic sinus and the thoraco-abdominal aorta, and were less inflammatory compared to plaques of Trem-1+/+ chimeric mice. Genetic invalidation of Trem-1 led to alteration of monocyte recruitment into atherosclerotic lesions and inhibited Tlr4-initiated pro-inflammatory macrophage responses. Furthermore, we identified a critical role for Trem-1 in the upregulation of Cd36, thereby promoting the formation of inflammatory foam cells. Genetic invalidation of Trem-1 in Apoe-/-/Trem-1-/- mice or pharmacological blockade of Trem-1 in Apoe-/- mice using LR-12 peptide also significantly reduced the development of atherosclerosis throughout the vascular tree, and lessened plaque inflammation (Figure 1).

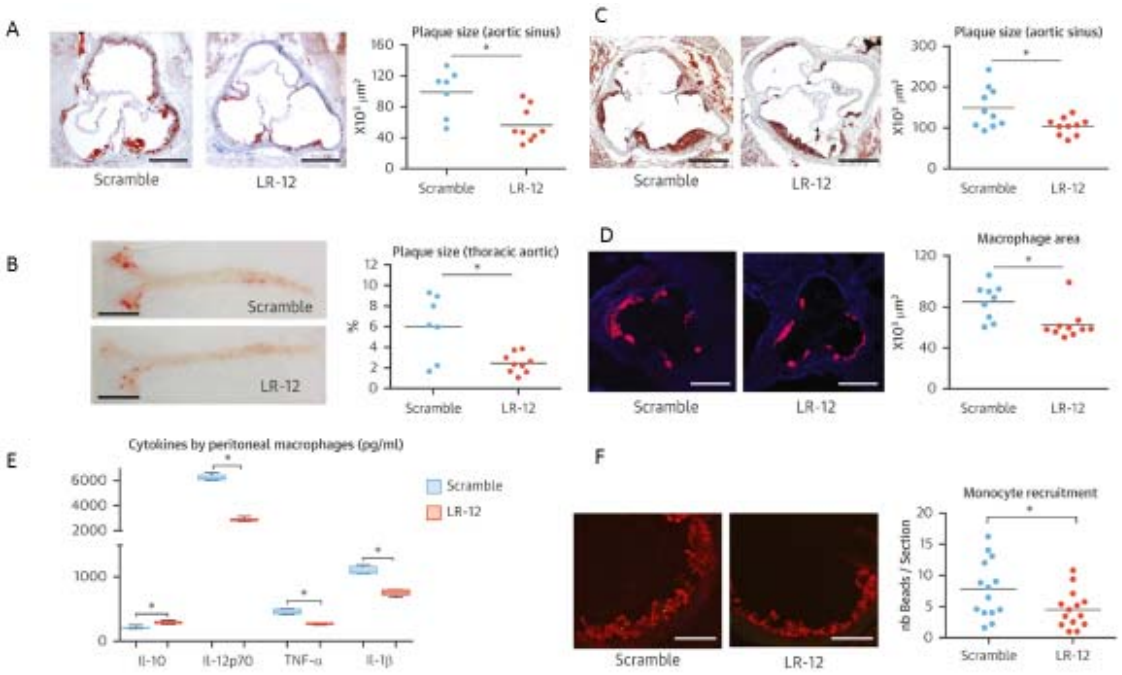
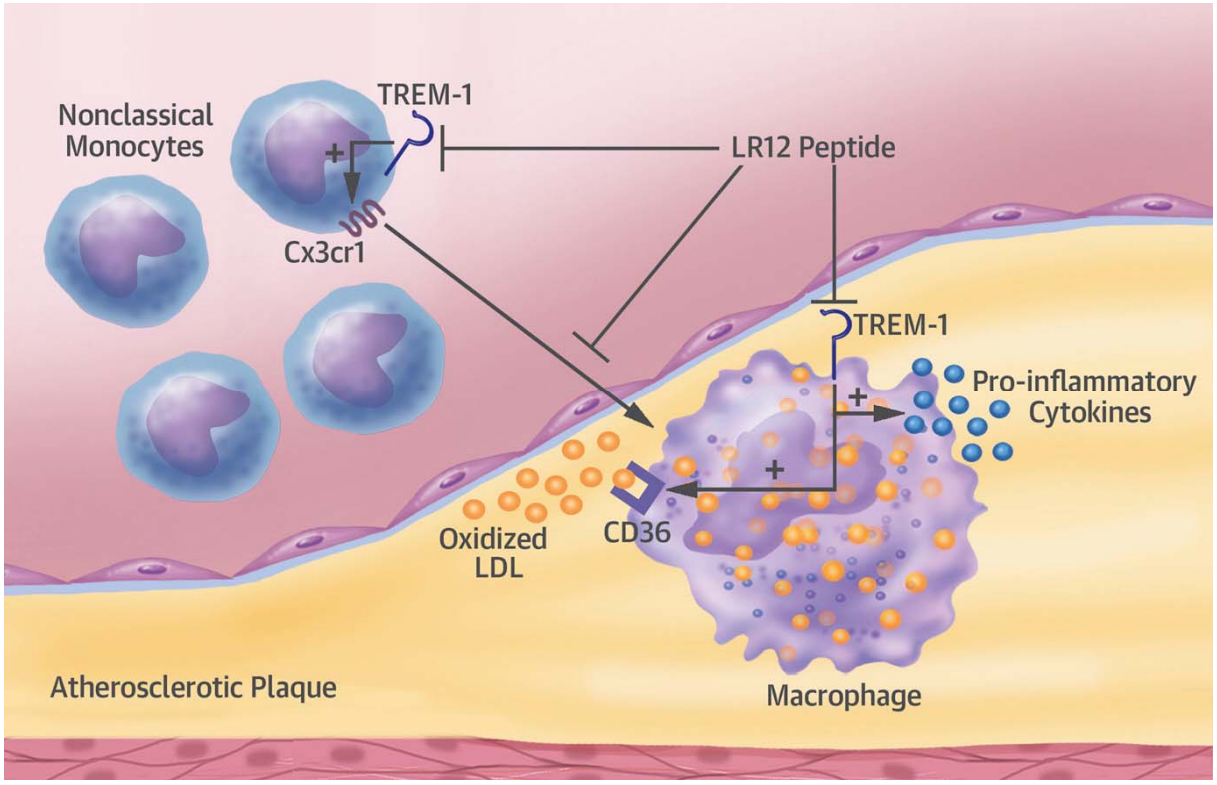


Figure 1 : The pharmacological inhibition of TREM-1 (LR-12) reduces the size of atherosclerotic lesions at an initiation stage (A, B) and during disease progression (C), with a reduction of plaque content in macrophages (D). This inhibition leads to reduce the secretion of pro-inflammatory cytokines by macrophages (E) and a decrease in monocytes recruitment in the plaques (F).

Those experimental datas have been reproduced on human macrophages. Moreover, TREM-1 was expressed in human atherosclerotic lesions mainly in lipid-rich areas, with significantly higher levels of expression in atheromatous compared to fibrous plaques.

Conclusion: We identify TREM-1 as a major upstream pro-atherogenic receptor. We propose that TREM-1 activation orchestrates monocyte/macrophage pro-inflammatory responses and foam cell formation through coordinated and combined activation of CD36 and TLR4. Blockade of TREM-1 signaling may constitute an attractive novel and double-hit approach for the treatment of atherosclerosis.



Summary : The activation of TREM-1 orchestrates the recruitment of non-classical monocytes into the plaque, the formation of foam cells and the production of pro-inflammatory cytokines by macrophages. Also blocking TREM-1 could be an attractive multi-target approach to prevent course of atherosclerosis.