I012
TRANSFORMING GROWTH FACTOR-BETA ACTIVITY IN MACROPHAGES PROTECTS FROM ANGIOTENSIN II-INDUCED AORTIC ANEURYSM IN MICE
Y. WANG 1, H. AIT-OUFELLA 1, O. HERBIN 1, J. HUANG 1, P.-L. THARAUX 1, A. TEDGUI 1, Z. MALLAT 1
1 Inserm, Paris, France

Background — Complicated aortic aneurysm is a major cause of mortality in elderly men. The critical pathophysiological mechanisms responsible for disease development and complications remain largely unknown. Mutations in transforming growth factor (TGF)-β receptor type II are associated with familial forms of the disease, and increased angiotensin II (AII)-dependent TGF-β activity has been directly linked to aortic aneurysm formation in a mouse model of Marfan syndrome. However, the direct role of TGF-β signaling in common forms of the disease has not been assessed.

Methods and Results — All-induced abdominal aortic aneurysm (AAA) is a validated model of aneurysm formation in mice, and is prevented, like murine Marfan syndrome, by treatment with angiotensin II receptor type 1 antagonists. Normocholesterolemic C57Bl/6 mice are resistant to All-induced AAA. Here, we show that systemic neutralization of TGF-β activity leads to unexpected and marked increase in the susceptibility of these mice to All-induced AAA (from -10% to 92.5%, n=40). These AAA display a large spectrum of complications on echography, including thrombosis, fissuration, false channel formation and rupture, leading to a high level of mortality (65%). Unexpectedly, the disease and its complications were refractory to inhibition of IFN-γ (n=10, 100% AAA), deletion of IL-4 (n=10, 80% AAA) or deletion of T and B lymphocytes (n=22 Rag-/- mice, 77.5% AAA). Interestingly, depletion of circulating monocytes for 14 days using clodronate liposomes completely prevented AAA formation (0% AAA in clodronate group vs 60% AAA at day 14 in the group without clodronate).

Conclusions — This study identifies a major protective effect of TGF-β activity against AngII-induced AAA, through modulation of monocyte/macrophage function.