

THE TRANSCRIPTOME PROFILING OF DISEASED MOUSE AORTAS DISCLOSES A DYSREGULATION OF THE SYMPATHETIC NEUROTRANSMISSION IN ATHEROSCLEROSIS

Elsa Franchi, Alice Colombo, Stefano Manzini, Giulia Chiesa, Marco Busnelli

Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, Milano, Italy.

Aim. Previous reports have suggested an association between the development of atherosclerosis and alterations in the aortic sympathetic nervous system, located in the adventitial layer. In a recent study, an increased adventitial axon density in proximity to advanced atherosclerotic plaques of Apoe-deficient mice was observed.

Methods. Eight-week-old C57Bl/6J control mice (Bl/6), Apoe knockout mice (EKO), EKO mice overexpressing human apoA-I (EKO/hA-I) and double Apoe/Apoa1 knockout mice (DKO) mice were fed a standard rodent diet or a Western-type diet for 22 weeks. At the end of the dietary treatment the aortic atherosclerosis was quantified, and a high-throughput sequencing approach was used to analyze the aortic transcriptome.

Results. On standard rodent diet no atherosclerosis was detectable in EKO/hA-I aortas and a moderate plaque development was observed in EKO and DKO, whereas Western-type diet increased plasma cholesterol levels, led to atherosclerosis development in EKO/hA-I and worsened that in EKO and DKO. The administration of Western-type diet deeply modified the aortic transcriptome. In the three genetically modified mouse lines, an upregulated expression of genes associated with the immunomodulatory response was observed. This was paralleled by a downregulated expression of genes involved in the activity of the aortic sympathetic nervous system. Functional enrichment analysis indicated that the presence of advanced atherosclerosis was accompanied by reduced neuronal generation, modulation of synapse chemical transmission, and catecholamine biosynthesis.

Conclusions. A relationship exists between atherosclerosis, dyslipidemia, and sympathetic neurotransmission. Advanced lesions are associated with reduced transcriptional activity related to sympathetic innervation of the aorta.