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Titolo	USE OF GENETICALLY MODIFIED MICE TO STUDY THE ANTI-INFLAMMATORY AND IMMUNOMODULATORY ROLE OF HIGH-DENSITY LIPOPROTEINS DURING ATHEROSCLEROSIS DEVELOPMENT [Tesi di dottorato]
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Sommario	Introduction: High-density lipoproteins (HDLs) have several anti-atherosclerotic/anti-inflammatory properties and the apolipoprotein A-I (apoA-I), the main protein component of HDL, plays a major role. The aim of the present project was to investigate the impact of apoA-I on atherosclerosis development, phenotype and inflammation, through the use of genetically modified mice. Methods: This study was performed in C57Bl/6 wild-type mice, resistant to atherosclerosis development, and in three athero-prone mouse lines: apoEKO, apoEKO with the additional deletion of murine apoA-I (dKO) and dKO overexpressing human apoA-I (hA-I). These animals were fed a chow diet for 22 weeks. Cholesterolemia was quantified by FPLC analysis; atherosclerosis development was evaluated at the whole aorta by en-face analysis and at the aortic sinus and common coronary arteries by histology. Skin biopsies were processed for both light (LM) and transmission electron microscopy (TEM); moreover, lipids were extracted from skin and the lipid content were quantified. Finally, skin draining lymph nodes and spleens were harvested for histology and leukocyte populations were investigated by flow cytometry. Results: As expected, in wild-type mice all the cholesterol was found

	into the HDL fractions and in apoEKO mice the majority of cholesterol was present into the VLDL/LDL fractions. In dKO animals HDL-cholesterol was instead almost absent and VLDL/LDL-cholesterol was about 30% lower compared to apoEKO mice. hA-I mice were characterized by a large HDL-cholesterol peak and by a marked presence of VLDL/LDL particles although less prominent that in apoEKO mice. En-face analysis showed that dKO and apoEKO mice had a similar extent of atherosclerotic plaques at the aortic arch (6.9 Â±5.6%, 7.2Â±5.5%, respectively). No atherosclerosis was instead observed in wild-type as well as in hA-I mice. At the aortic sinus, dKO mice showed a significant increase in lesion development compared to both apoEKO and hA-I mice (6.2Â±0.5x105?m2 vs. 3.2Â±0.7x105?m2 and 0.4Â±0.3x105?m2, p<0.001). As expected, no atherosclerotic plaques were found at this district in wild-type mice. In addition, preliminary data suggest that dKO, but not apoEKO mice develop significant atherosclerotic plaques at the common coronary arteries (76,25Â±8,62% and 0Â±0%, respectively). LM analysis displayed that the skin of EKO and h-A-I mice was comparable with C57Bl/6 mice, whereas dKO animals showed an increase in dermal thickness and the presence of foam cells and lymphocytes in reticular dermis. TEM analysis revealed the accumulation of cholesterol cleft in the papillary dermis and of cholesterol crystals within foam cells. Quantification of the skin lipid content showed a strong accumulation of both unesterified and esterified cholesterol in dKO mouse skin. The weights of skin lymph nodes in dKO mice were higher compared to those of the other mouse lines. Histological analysis showed the presence of foamy macrophages, granulomatous reactions surrounding cholesterol crystals and dilated sinuses. Conversely, spleen weight and histology were unaffected by genotypes. In peripheral blood, skin draining lymph nodes and spleen, dKO mice showed a significantly higher percentage of CD4+ T effector memory lymphocytes and a reduced percentage of T naÃ¯ve lymphocytes compared to other experimental group. The percentage of monocytoid or plasmacytoid dendritic cells, B lymphocytes and monocyte subsets in secondary lymphoid organs were not influenced by the genotype. Conclusion: Taken together our results demonstrate that murine apoA-I deletion into an apoEKO background markedly exacerbates atherosclerosis development both at the aortic sinus and common coronary arteries. ApoA-I deficiency is associated with an impaired cholesterol homeostasis in the skin. This model reproduces for the first time the cutaneous phenotype of human apoA-I deficiency, characterized by xanthomatous deposition in the absence of a hyperlipidemic status. In addition, our data show that apoA-I deletion is related to an enlargement of skin draining lymph nodes which are characterized by foamy macrophages accumulation and cholesterol deposition, predisposing to granulomatous reactions. Finally, the new murine model displays activation and increase in CD4+ T effector memory lymphocytes in peripheral blood and lymphoid organs.
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