Immune-metabolic characterization of a humanized mouse model for translational studies on cardiovascular diseases

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Background: Atherosclerosis represents one of the main cardiovascular risk factors and is driven by high plasma cholesterol levels and an impaired immuno-inflammatory response. Despite effective lipid-lowering therapies, some patients exhibit persistent residual inflammatory risk, highlighting the need for experimental models that enable the translation of molecular mechanisms and immunomodulatory cardiovascular therapies from preclinical to clinical studies. In this context, we present the immuno-metabolic characterization of an immunodeficient mouse model with an atheroprone genetic background, whose immune system is reconstituted with human hematopoietic stem cells (CD34+).

Metodi: Humanized TKO-LDLr KO mice (obtained by crossing LDLr KO mice with immunodeficient Rag2-KO/IL2rg-KO/CD47-KO mice, HuTKOL) were generated by irradiating 2-3-day-old pups at low doses (250cGy), followed by intrahepatic injection of commercial human CD34+ cells or those derived from iPSCs (250,000-300,000 cells/mouse). After 12 weeks, human cell engraftment was assessed by FACS. The HuTKOL mice were then fed a high-cholesterol Western-type diet (WTD) for 12weeks to study the immuno-metabolic phenotype and atherosclerosis development.

Risultati: HuTKO-L mice showed good engraftment of commercial human CD34+ cells in circulation (%hCD45+/total live leukocytes: 40.97%,SE±3.46%). B-lymphocytes were the most abundant population at 8 weeks (%hCD19+/hCD45+:72.81%,SE±2.33%),but decreased progressively (%hCD19+/hCD45+: 13.85%,SE±2.98%), while T-lymphocytes showed the opposite trend, becoming the dominant population after 12 weeks of WTD (%hCD3+/hCD45+: 58.84%,SE±4.86%). Exposure to WTD induced dyslipidemia (plasma cholesterol: 1086.90mg/dl,SE±65.15) and atherosclerosis (%plaque obstruction in the aortic root: 24.79%,SE±3.17%; atherosclerotic lesion volume: 0.32mm^3; %fibrosis/plaque area: 33.94%,SE±16.17%), with infiltration of human immune cells into the plaques. Furthermore, WTD feeding induced the expansion of CD4-memory T-lymphocytes and the production of IgM against atherosclerosis-associated antigens. Characterization of iPSC-derived CD34+ cells and their engraftment in TKO-L mice is currently ongoing.

Conclusioni: HuTKOL mice represent a tool for studying the dynamics of human adaptive immunity under dyslipidemic conditions and for testing immunomodulation strategies in cardiovascular diseases.