The vascular autoimmunosome: a game changer for the concept of the buildup of atherosclerotic plaque?

Aksam J. Merched,[*,†,1] **Danièle Daret,**[‡] **Lan Li,**[†] **Nathalie Franzl,**[‡] **Maria Sauvage-Merched**[§]

*Department of Pharmaceutical Sciences, and INSERM U1053, Bordeaux, France; [†]Department of Cell Biology, Baylor College of Medicine, Houston, TX, USA; [‡]INSERM U1034, Pessac, France and [§]Children University Hospital of Bordeaux, Bordeaux, France

Aims: Higher cardiovascular morbidity in patients with wide range of autoimmune diseases highlights the importance of autoimmunity in promoting atherosclerosis. The present study was designed to evaluate the autoimmune component of atherogenesis and identify putative antigens that may trigger the autoimmune reactions.

Methods: We created a mouse model of autoimmunity-associated atherosclerosis by transplanting bone marrow from FcRIIB$^{-/-}$ mice to LDL receptor knockout mice. This approach combined 2 genetic backgrounds associated with lupus and atherosclerosis. We characterized the cellular and molecular mechanisms of atherogenesis and identified specific autoantigens in the vascular wall using serologic proteomic studies.

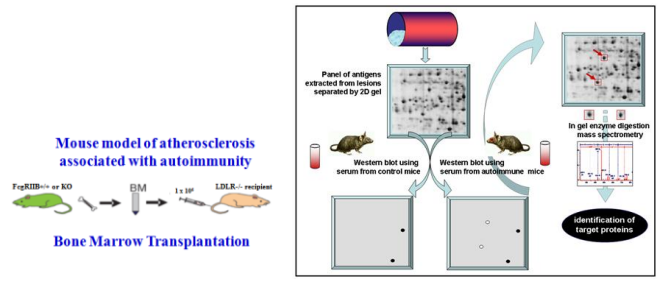

Figure 1. Creation of mouse model by bone marrow transplantation and schematic of proteomic approach. Panels of antigens in atherosclerotic lesions are obtained using 2-D PAGE. Proteins are transferred onto PVDF membranes for Western blotting with sera or purified IgG from autoimmune mice (FcgRII$^{-/-}$, LDLR$^{-/-}$) and control mice (LDLR$^{-/-}$). Proteins specifically reacting with sera from autoimmune mice (shown in open circle) will be localized within the 2D panel (arrows), excised, and identified by mass spectrometry.

Results: At the cellular level, FcRIIB-deficient macrophages showed significant reduction in phagocytic capabilities. Proteomic analysis revealed circulating autoantibodies in autoimmune mice that targeted 25 atherosclerotic lesion proteins which we called the "vascular autoimmunosome". These targets include essential components of adhesion complex, cytoskeleton and extracellular matrix, and proteins involved in critical functions and pathways. Microscopic examination of atherosclerotic plaques revealed essential colocalization of autoantibodies with endothelial cells, the extracellular matrix at the multilayer junctions, and necrotic cores. Our findings show that defects in housekeeping activities linked to phagocytosis may exasperate immune reactions and trigger autoimmunity.

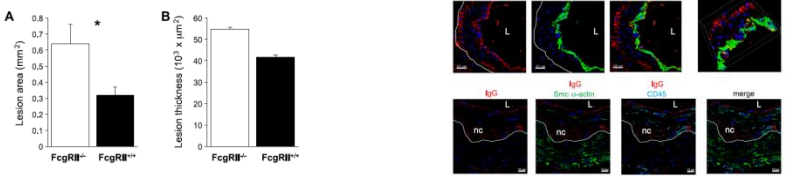

Figure 2. FcRIIB deficiency significantly accelerated atherosclerosis (A, B). Immunohistochemical staining of mouse IgG in an aortic atherosclerotic lesion (C) revealed a distribution of 2 layers of IgG located at the ECs (CD31 marker), necrotic core, and the internal elastic lamina.

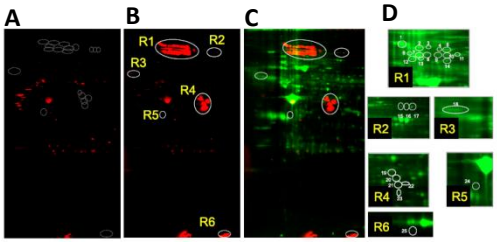

Figure 3. A) Immunoreactivity of control sera (FcRIIB+/+). **B)** Immunoreactivity of autoimmune serum (FcRIIB$^{-/-}$). 5 regions (R1 to R5) are outlined, representing specific or highly immunoreactive spots recognized by autoimmune sera. **C)** superimposed autoimmune immunoblot image . **D)** Highlights of 5 immunospecific regions superimposed onto a preparative gel , from which 25 immunoreactive spots were excised for identification by mass spectrometry.

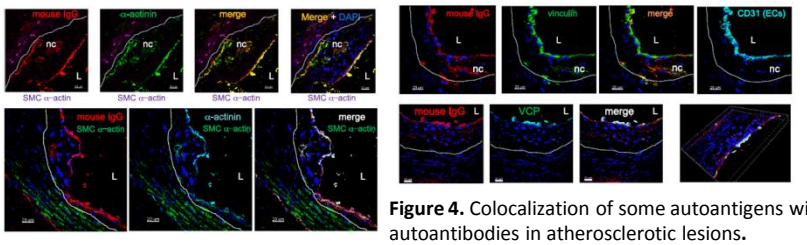

Figure 4. Colocalization of some autoantigens with autoantibodies in atherosclerotic lesions.

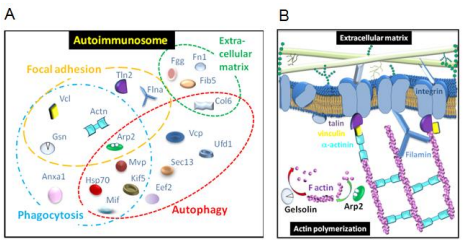

Figure 5. The vascular autoimmunosome. (**A**) Vascular autoimmune targets were classified into 4 major groups indicated in circles. (**B**) Organization of focal adhesion complex of actin interacting proteins.

Conclusions: The discovery of the vascular autoimmunosome supports the concept that autoimmunity is the driving force behind the buildup of atherosclerotic plaques in varied autoimmunity-associated diseases. Indeed, autoantibodies to damaged or modified endothelial cells structures may provide a foundation for the buildup of atherosclerotic lesions, and continuous challenges by the immune system may become the continual seeding of a growing, dynamic plaque. The vascular autoimmunosome may be a useful target for diagnostic and immunotherapeutic interventions in autoimmunity-associated diseases that have accelerated atherosclerosis.

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