INSTITUTE OF CELLULAR BIOLOGY AND PATHOLOGY 'NICOLAE SIMIONESCU'

OF ROMANIAN ACADEMY

Pathophysiology and Pharmacology Department

HABILITATION

"VASCULAR ENDOTHELIAL DYSFUNCTION: CARDIOVASCULAR RISK FACTORS, NEW BIOMARKERS AND THERAPIES"

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ABSTRACT

The Habilitation Thesis reflects the author's activity performed between 2005 and 2013 years, after PhD thesis, and it is based on the original contributions achieved during research activities in the Institute of Cellular Biology and Pathology Nicolae Simionescu of Romanian Academy. Also, there are highlighted author's managerial competence, presentation ability and future perspectives in research and academic field.

The author's researches in the field of cardiovascular disease bring new scientific contributions for a better understanding of the vascular dysfunction, cardiovascular risk factors, cellular and molecular biomarkers and corresponding therapy.

Vascular endothelial dysfunction is a well established response to cardiovascular risk factors, which precedes the development of atherosclerosis, diabetes and obesity and represents a challenging clinical problem. The term endothelial dysfunction refers to a condition in which endothelium loses its physiological ability to promote vasodilation, fibrinolysis and anti-aggregation. The responsible factors for the endothelial dysfunction are vasodilators (nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor (EDHF)), and vasoconstrictors (superoxide anions, endoperoxides, thromboxane A2, endothelin-1, and angiotensin II). Endothelial activation represents a switch of the normal quiescent phenotype to a synthetic, proliferative, and inflammatory one. The cardiovascular risk factors such as hypercholesterolemia, hypertension, and hyperglycemia, as well as other inflammatory conditions activate molecular machinery in the endothelium that results in expression of chemokines, cytokines, and adhesion molecules designed to interact with leukocytes and platelets and target inflammatory process.

The cell-derived microparticles (MPs) and circulating endothelial progenitor cells (EPCs) have recently generated great attention as potential novel diagnostic/prognostic biomarkers for vascular integrity and therapeutic clinical approaches, and the use of these cells are ongoing. MPs are extracellular membrane vesicles released from normal, apoptotic and pathological cells following a process of detachment from cells of origin. MPs are typically defined by their size (100 nm – 1000 nm), exposure of phosphatidylserine (PS), the expression of surface antigens, proteins and genetic material, originating from their donor cells, and as important vehicles of intercellular communication across numerous biological processes. The increased numbers of circulating MPs have been implicated in many cardiovascular diseases, but their pathophysiological role has not been fully investigated yet. EPCs are known to be released from bone marrow, fat tissue, vessel wall (especially adventitia) and possibly spleen, liver and intestine. EPCs enter the blood as circulating EPCs, where they express CD133 (at the early stage), then CD34/Flk-1, and also VEGFR2. EPCs as defined by the depicted markers can be further mobilized to contribute to endothelial repair, but can also promote plaque growth, neovascularisation and instability. Clinically, the number and function of EPCs may reflect the balance between endothelial integrity and repair, both measures have been suggested as surrogate markers of endothelial function and cardiovascular diseases. When cardiovascular risk factors are treated with specific drugs such as enoxaparin or nebivolol only a part of the endothelial dysfunction could be reversed. Also, the use of antioxidants and/or other medications, such as prostacyclin, statins, ACE inhibitors, AT II inhibitors, like irbesartan, can enhance EPCs number and function and reduce MP release. Another approach to improve the vascular dysfunction

could be the therapy developed by using MP and EPC transplantation. Thus, there are some strategies proposed based on MP and EPC therapeutic potential in the restablishment of endothelial dysfunction and their use for vascular regenerative medicine.

In conclusion, the purpose of author's studies was to uncover at cellular and molecular level the pathobiochemical alterations occurring in the blood vessels, which lead to atherosclerosis, diabetes, obesity, ageing, metabolic syndrome. Publications were in the field of endothelial function/dysfunction, endothelial vasoactive factors, MPs and EPCs as a signature of vascular dysfunction and a repair mechanism in cardiovascular diseases. The major contributions concern: **1.** the study of cellular and molecular mechanisms involved in vascular dysfunction in diabetes and obesity and in the effect of some drugs (nebivolol); **2.** the regulation of endothelial dysfunction by NO, endothelium-derived contracting and relaxing factors and antihypertensive (nebivolol, irbesartan) and antithrombotic (enoxaparine) drugs; **3.** the contribution of cardiovascular risk factors, circulating MPs and EPCs to endothelial dysfunction as a new biomarkers with potential pronostic value for cardiovascular disease; **4.** the investigation of dual behaviour of circulating platelet microparticles (PMPs) as biological effectors with important role in the vascular patho-physiology and as endogenous triggers of EPCs to facilitate endothelial reconstruction and repair in the experimental induced vascular atherosclerosis

The knowledge and results accumulated so far represent a strong motivation to continue the efforts to unravel the cellular and molecular mechanisms involved in the cardiovascular disease and help finding drugs and other complementary approaches, to correct them in diseases afflicting many people.