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Aktywność komórek progenitorowych śródbłonka w nadciśnieniu tętniczym

Summary

Endothelial cells are responsible for regulation of: blood pressure, immune response, new blood vessel formation or remodelling of already existing vessels. Alterations in the function of vascular endothelium are connected with pathophysiology of numerous disorders, with endothelium as a system subjected to damage as well as factor involved in generation of such changes. One of the most important features of vascular system is the ability to adapt its structure to new requirements and stimulus through the modification of endothelial cells activity.

In 1997 Asahara et al. described population of blood cells with the CD34+VEGFRII+ phenotype being capable to differentiate into mature endothelial cells – population was referred to as EPCs - Endothelial Progenitor Cells. Further tests exhibit that these cells participated in regeneration of disturbed endothelium and new vessels formation. Bone marrow has been recognized as a main source of EPCs.

Low number of circulating endothelial progenitor cells is described as a new risk factor for development and progression of cardiovascular diseases - in individuals characterised by diminished population of these cells neovascularisation and regeneration processes progress with lower effectiveness.

Commonly analyzed phenotypes of EPCs are CD34+VEGFRII+ and CD34+VEGFRII+CD133+, nevertheless there are some publications suggesting that the presence of other molecules like: receptor for stem cell factor – c-Kit, receptor for stromal cell-derived factor 1– CXCR4 or even nitric oxide production are indicators whether cell belongs to the EPC "family". These compounds have also crucial impact on cell function.

It is accepted that cardiovascular disease risk factors, especially when present simultaneously, reduce population quantity or exhibit different, negative effect on progenitors function.

Hypertension is a cardiovascular system disease, characterised by elevated values of arterial pressure above 139 mmHg for systolic blood pressure and/or 89 mmHg for diastolic blood pressure. The most common complications associated with the disease are: stroke, coronary artery disease or chronic kidney disease as a result of endothelium damage. Hypertension itself is the most important factor for premature death.

One may presume that impairment of endothelial progenitors occurs in hypertension as dysfunction of mature endothelial cells is characteristic for this disease. It is speculated that the dysfunction of mature endothelium or rarefaction of blood vessels and small arteries observed in hypertensive individuals may be the result of EPC pool exhaustion.

Therefore, the purpose of this dissertation was to analyze whether hypertension occurrence affects the population of CD34+ and CD34+VEGFRII+ progenitor cells. Moreover, the goal of this thesis was to determine how long-term hypertension therapy and some chosen factors affect profile of CD34+ and CD34+VEGFRII+ progenitor cells. In this dissertation we aimed to answer the question whether successful hypertension therapy normalize number and features of CD34+ and CD34+VEGFRII+ cells.

69 individuals with primary arterial hypertension who were patients of: 7th Navy Hospital in Gdańsk, non-public Health Center "Medicus" and Department of Cardiac Diagnostics, 2nd Chair of Cardiology of Medical University of Gdańsk were involved in the project. 19 of these patients were diagnosed with hypertension during inclusion into the analyzes, whereas remaining 50 patients were subjected to long-term anti-hypertensive therapy. Control group comprised of 38 healthy volunteers in comparable age, who reported to the family doctor and were not diagnosed with cardiovascular diseases. Material for the analyzes comprised of venous blood.

The experiments were pertformed with flow cytometry analyzes of whole blood cells with the use of surface markers such as: CD34, VEGFRII, CD133, c-Kit, CXCR4 as well as analyzes of nitric oxide production, through the use of specific fluorescent dye. Cells were analyzed as CD34+ and CD34+VEGFRII+ populations that differ in the presence/absence of remaining factors. Immunoenzymatic tests allowed to determine concentrations of angiotensin II and sICAM-1 in blood sera of patients and controls.

Obtained results indicated, inter alia, that:

- arterial hypertension occurrence is connected with an increased number of progenitor cells from the CD34+ and CD34+NO+ populations, as well as CD34-positive cells lacking the expression of CD133 glycoprotein
- in patients with newly-diagnosed hypertension we observed increase in the population of CD34+VEGFRII+c-Kit+(NO)+ cells - progenitor cells from endothelial linage that are susceptible to mobilisation and able to produce nitric oxide
- in patients with newly-detected illness there is also greater population of cell with CD34+VEGFRII+CXCR4+NO+ phenotype, thus precursor cells equipped with chemokine receptor allowing their migration into damaged/remodelled vessels

- numerous correlations between analyzed cells and concentration of angiotensin II indicate that this peptide is connected with populations of CD34+ and CD34+VEGFRII+ cells in a case of newly-developed arterial hypertension.

In a case of patients with treated perennial hypertension we observed:

- re-enactment of, inter alia, CD34+ and CD34+CD133- populations sizes to values observed in healthy group
- increased levels of endothelial damage marker (s-ICAM-1) in blood of patients treated for arterial hypertension correlates with the decrease, below the values characteristic for healthy individuals, of numerous CD34+ and CD34+VEGFRII+ progenitor cell populations
- long-term hypertension therapy exposes alterations characteristic for aging – number of CD34+VEGFRII+ cells, co-expressing CD133 and c-Kit+ markers as well as their NO-producing subpopulations decreased with age
- increasing risk for other cardiovascular diseases development in patients with arterial hypertension is connected with the reduction of CD34+VEGFRII+CD133+ and CD34+VEGFRII+c-Kit+ cells and their NO-producing subpopulations
- ineffective arterial hypertension therapy is associated with decrease of CD34+VEGFRII+ and CD34+VEGFRII+CD133+ cell populations and severe reduction of CD34+VEGFRII+c-Kit+ and CD34+VEGFRII+CXCR4- cells to levels that prevent reliable enumeration

This allows us to deduce, that hypertension occurrence is connected with the release mobile progenitor cells from endothelial linage. These cells are able to produce nitric oxide and migrate to damaged/remodelled vessels. Angiotensin II seems to be one of the factors that induce such alterations in a case of newly-detected hypertension. Long-term arterial hypertension therapy results in the restoration of correct number of CD34+ and CD34+CD133- cells, but simultaneously exposes deficiency in progenitors cells like: CD34+VEGFRII+CD133+, CD34+VEGFRII+c-Kit+ and their nitric oxide-producing counterparts. It seems therefore that therapy do not eliminate growing endothelial damage. Deteriorating patients clinical status is an independent factor connected with the risk of endothelial progenitor cells deficiency. Ineffective therapy not only fails to reduce arterial pressure to required values, but is also associated
with drastic deficiency of endothelial progenitors such as CD34+VEGFRII+c-Kit+ and CD34+VEGFRII+CXCR- cells, which may impede endothelial regeneration.

Effective hypertension therapy do not regenerate cells able to restore vascular endothelium completely, but ineffective therapy is connected with drastic progenitor cell deficiency.