Treatment-Sensitive Premature Renal and Heart Senescence in Hypertension

Martin W. Bergmann, Laura Zelarayan, Christina Gehrke

Hypertension-induced renal and heart failure account for a large proportion of chronic disease burden in the elderly. Antihypertensive therapy may halt the progression of disease. Preventing organ damage has emerged as a primary target for new approaches to treat hypertension. Signaling pathways affected by hypertension but not necessarily involved in blood pressure regulation itself have been identified as attractive new targets.

Already in the early 1960s, a cellular stopwatch was described, which induced a growth arrest of normal somatic cells after several rounds of cell division in culture. In contrast, cancer cells were found to proliferate unlimited, implicating cellular senescence as an important molecular mechanism of protection against cancer. The molecular and cellular pathways controlling senescence have since been identified. The 3 “Hayflick factors” recording the proliferative history of cells and tissues are telomere shortening, accumulation of damaged DNA plus chromosomal damage, as well as derepression of the INK4a/ARF genomic locus. The molecular pathways mediating senescence, namely, telomere shortening and expression of p16INK4a through stress and aberrant signaling–induced senescence are dissociated, indicating independent pathways.1

On a cellular level, a picture is emerging that tissue senescence is not only about the differentiated cells having a limited life span but also, and possibly even more important, reduced regenerative capacity of organ-resident stem cells.2 Although telomere shortening records cell division and finally leads to activation of the p53 pathway inducing apoptosis, the cell-cycle inhibitor p16INK4a may directly affect regenerative and proliferative activity of organ-resident stem cells because of inhibition of cyclin-dependent kinases 4 and 6. Evidence for the importance of this pathway was well proven concerning β-cell precursors in pancreatic islets accounting for the development of late-onset diabetes type II. Also, aging hematopoietic stem cells demonstrate reduced lymphoid lineage potential.3–5 Genetic evidence suggests that hair graying is the result of increased apoptosis of melanocyte stem cells in their niche.6 Aging is also associated with a decline in neuronal progenitor cell proliferation because of increased expression of p16INK4a in neuronal precursor cells located in the subventricular zone.7

It is in this context that the study by Westhoff et al8 adds an intriguing new twist to the understanding of hypertension-induced organ damage. Although an association of p16INK4a expression and hypertension-induced renal and heart failure had been described before, the investigators now provide compelling evidence of preventing premature tissue senescence by antihypertensive treatment. A classical blood pressure–lowering therapy affecting vasotonus but also monotherapy with either spironolactone or losartan prevented organ damage in association with the downregulation of p16INK4a. These data suggest a possible “antiaging” effect of antihypertensive therapy. Whether this also implies an effect of hypertension on the regenerative capacity of organ-resident stem cells currently remains unclear.

The authors analyzed 2 established animal models of hypertension, namely the deoxycorticosterone acetate-salt rat model and transgenic rats heterozygous for the mouse Ren-2gene. The latter are regarded as a valid model for angiotensin II–mediated hypertension. Hypertensive tissue injury was accompanied by a time-dependent, significant increase of nuclei positive for phosphorylated p38 mitogen-activated protein kinase and p16INK4a (see scheme in Figure). p38 mitogen-activated protein kinase was analyzed because of its role in stress-induced p16INK4a expression: derepression of the INK4a locus by reactive oxygen species leading to limited functionality of hematopoietic stem cells is controlled by p38 mitogen-activated protein kinase.9 Similar observations were made in myocardium and cardiac vasculature. In addition, the investigators analyzed tissue samples from 9 patients, who received clinically indicated diagnostic kidney biopsies and had documented hypertensive renal disease. Again, the number of p16INK4a-positive nuclei was increased when expression levels were compared with a published, age-dependent regression analysis.

Classical antihypertensive treatment combining hydrochlorothiazide, hydralazine, and reserpine or treatment with spironolactone prevented both hypertensive-induced organ damage and p16INK4a expression. Similarly, losartan also prevented both angiotensin II–induced organ damage and p16INK4a expression in the Ren-2gene model. In summary, p16INK4a expression tightly correlates with hypertensive tissue damage both in experimental models and human samples. Treatment prevents both organ damage and p16INK4a expression (see scheme in Figure).

Building on these results, the question arises regarding whether p16INK4a expression is merely a marker of damage and premature senescence or an effector. Although the current

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From the Department of Cardiology (M.W.B., C.G.), Franz Volhard Clinic, Charité Campus Buch and HELIOS Kliniken Berlin, Berlin, Germany; Max Delbrück Center for Molecular Medicine (L.Z.), Berlin, Germany

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study does not address this issue, several recent publications have shed light on this issue in other tissue compartments. At young age, expression from the INK4a locus is repressed by polycomb transcription factors. Mice lacking p16\(^{INK4a}\) have an increased capacity of regeneration, whereas constitutive p16\(^{INK4a}\) expression blocks endogenous regeneration.\(^2\) This observation was most clearly documented again concerning the /H9252-rep cells in the pancreatic islet but may also affect other tissue compartments. In addition, large population-based studies have found a clear association of single nucleotide polymorphisms in the INK4a/ARF locus and early onset diabetes and vascular heart disease.\(^2\)

Concerning hypertension-induced heart failure, the study by Westhoff et al\(^8\) is also intriguing: the balance among apoptosis, hypertrophy, and endogenous regeneration of cardiomyocytes is critical for cardiac tissue homeostasis.\(^9\) Telomere shortening as the other senescence marker has been described as a hallmark of heart failure even in postmitotic cells: cardiac apoptosis in human heart failure was associated specifically with defective expression of the telomere repeat-binding factor TRF2, telomere shortening, and activation of the DNA damage checkpoint kinase, Chk2.\(^10\) Therefore, further studies assessing senescence markers and their role as effectors in heart failure development are also needed.

Tissue-specific stem cells have also been detected in the kidney, although their role in regenerating different tissue compartments is less clearly characterized. Pharmacological therapies aiming at enhancing endogenous regeneration by targeting the cell cycle machinery are under development.\(^11\)

As a note of caution, however, the lack of specific markers of resident stem cells currently limits any definite conclusion. Nevertheless, the current debate concerning the cellular and molecular pathways of senescence might also be valid for the understanding of hypertensive renal and heart disease.

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**References**

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