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Therapeutic potential of Navitoclax in age-related cardiovascular diseases

Anna Walaszczyk, PhD,

Cardiovascular Research Centre

Biomedical Institute

Newcastle University

Newcastle upon Tyne, UK

Cardiovascular disease (CVD) is the leading cause of death in individuals over 60 years old. Aging is associated with an increased prevalence of coronary artery disease and a poorer prognosis following of acute myocardial infarction (MI). We have demonstrated that oxidative stress induces myocardial senescence, which is a major contributor to impaired function. In aged mice, prophylactic treatment with the senolytics drug navitoclax reduces senescence and the expression of SASP associated proteins resulting in attenuated age-related myocardial remodelling and improved survival and functional outcome following MI. In young animals, navitoclax treatment following MI with reperfusion improved left ventricular function, increased myocardial vascularization, and decreased scar size. SWATH-MS based proteomics revealed that elimination of senescent cells attenuated biological processes associated with maladaptive remodelling including fibrosis and inflammation. Cytokine array demonstrated navitoclax reduced expression of proinflammatory, profibrotic and anti-

angiogenic cytokines, including interferon gamma-induced protein-10, TGF-ß3, interleukin-11, interleukin-16 and fractalkine. Together our studies provide proof-of-concept evidence that cellular senescence and the proinflammatory SASP contribute to impaired heart function in multiple CVDs by promoting myocardial remodelling. Subsequently, senolytic treatment represents a potential novel therapeutic avenue to improve patient outcome for these CVDs.

SHORT BIOGRAPHY

EDUCATION:

2010 - 2014: Ph.D. in Medical Biology Centre for Translational Research and Molecular Biology of Cancer, MSC Cancer Centre and Institute of Oncology, Gliwice Branch, Poland Title: Radiation induced cell and tissue damages in mice hearts.

2000 - 2006: M.Sc. in Biology Faculty of Biology and Environmental Protection, University of Silesia, Poland Title: Cytogenetics comparative studies of meiosis in resynthesized and cultivated *Brassica napus L.*

POSITIONS HELD:

Present position:

Research Associate Cardiovascular Research Centre, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK (12.2016 - present)

Previous positions:

Research Associate Centre for Translational Research and Molecular Biology of Cancer, MSC Cancer Center and Institute of Oncology, Gliwice Branch, Poland (2014 – 2016)

Research Assistant Centre for Translational Research and Molecular Biology of Cancer, MSC Cancer Center and Institute of Oncology, Gliwice Branch, Poland (2010 – 2014)

Biologist Department of Experimental and Clinical Radiobiology, MSC Cancer Centre and Institute of Oncology, Gliwice Branch, Poland (2008 – 2010)

Trainee Department of Experimental and Clinical Radiobiology, MSC Cancer Centre and Institute of Oncology, Gliwice Branch, Poland (2007 – 2008)

RESEARCH SUMMARY:

During my PhD I analyzed radiation induced heart tissue damage which is one of the consequences of breast cancer treatment. Further, during my first PostDoc I extended this study towards radio- and chemotherapy impact on heart tissue. Results from both project did not show dose dependent tissue failure, but shown that combination of toxic agents leads to not only tissue damages but also to accumulation of senescence in heart tissue. In the mean time I took a part in projects describing mechanism of NF-kB pathway activation after ionizing radiation. I was also a part of

the team looking for new biomarkers of e.g. acute mucosal reaction in cancer patients. In 2013 I obtained founding to identify potential biomarkers of metastasis and relapse in breast cancer patients.

To extend my knowledge about senescence in heart tissue and myocardial dysfunction I started to work in Cardiovascular Research Centre, Newcastle University. During this post-doctoral position I described how clearance of senescent cells improves survival and recovery following myocardial infraction. As a part of a team I was also involved in project where we show impact of senolytics on ischemia – reperfusion injury model. In the meantime I was a member of a team that described mechanism of cardiomyocyte senescence.

After my first postdoctoral position in dr Richardson's laboratory we decided to continue working together and we extended our studies on human heart tissue.

PUBLICATIONS:

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4. Walaszczyk A, Gabrys D. Molecular markers used in breast cancer diagnosis – current practice and future perspectives. NOWOTWORY Journal of Oncology 2018, volume 68, number 5–6, 259–267; DOI: 10.5603/NJO.2018.0041

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lysosomes from liver of mouse irradiated in vivo. Int J Radiat Biol. 2018 doi: 10.1080/09553002.2018.1451005.

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8. Lysek-Gladysinska M, Wieczorek A, Walaszczyk A, Jelonek K, Jozwik A, Pietrowska M, Dörr W, Gabrys D, Widlak P. Long-term effects of low-dose mouse liver irradiation involve ultrastructural and biochemical changes in hepatocytes that depend on lipid metabolism. Radiat Environ Biophys. 2018 doi: 10.1007/s00411-018-0734-9.

9. Walaszczyk A,_Szołtysek K, Jelonek K, Polanska J, Kulik R, Doerr W, Haagen J, Widłak P, Gabryś D. Heart irradiation reduces microvascular density and accumulation of HSPA1 in mice. Strahlenther Onkol. 2018. doi: 10.1007/s00066-017-1220-z.

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