ESC European Society of Cardiology
Cardiovascular Research (2022) **00**, e1–e3
https://doi.org/10.1093/cvr/cvab366
SPOTTED BY THE SCIENTISTS OF TOMORROW
CARDIOVASCULAR RESEARCH Onlife

Old, but gold? Not the case for the immune system when promoting systemic ageing

Sveva Bollini [1]* **and Tomasz J. Guzik** [2,3]

[1]Department of Experimental Medicine (DIMES), University of Genova, L.go R. Benzi 10, 16132, Genova, Italy; [2]Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; and [3]Department of Medicine, Jagiellonian University College of Medicine, Krakow, Poland

Commentary on 'An aged immune system drives senescence and ageing of solid organs' by M. J. Yousefzadeh *et al.* 2021, *Nature*, 594(7861):100-105.

The saying 'the older, the wiser' may be appropriate for several aspects in everyday life, but a senescent immune system, according to a recent elegant study from Yousefzadeh *et al.*, may drive systemic ageing. The authors described a mechanism underlying the age-dependent decline in immune system function and immunosenescence and their detrimental effects on peripheral tissues. This novel mechanism was demonstrated using specific deletion of *Excision repair cross complementing-group 1* (*Ercc1*) in murine *Vav1*-positive haematopoietic precursors.[1] ERCC1, an endonuclease pivotal for DNA excision repair;[2] and the deficiency of the ERCC1–XPF complex increases tissue oxidative damage thus initiating cell senescence.[2,3] *Vav-iCre*$^{+/-}$; *Ercc1*$^{-/fl}$ mice presented accelerated ageing and premature immunosenescence characterized by progressive peripheral leukopoenia with lymph node atrophy and compromised cellular and humoural immune function starting prematurely, at 5 months of age. Splenocytes, bone marrow cells, and peripheral CD3+ cells from aged transgenic mice showed increased levels of *p21* and *p16* senescence markers, and senescence-associated secretory phenotype, when compared to the wild-type counterpart.

Activation of immunosenescence in the transgenic mice haematopoietic compartment induces systemic ageing and its hallmarks such as oxidative stress, increased expression of *p16* and senescence-associated β-galactosidase in the liver and kidney. Activation of tissue senescence was indeed conferred by immune cells, as transgenic splenocytes induced tissue p16 expression when transplanted into the *p16*^{Ink4a}-luciferase reporter mice. Interestingly, when young wild-type splenocytes were administered to a transgenic model of human progeroid syndrome (*Ercc1*$^{-/\Delta}$ mice), senescence and tissue damage were lowered in several tissues.

These findings are important, as they show that immune system dysfunction induced by impaired endogenous DNA repair in haematopoietic progenitors, can trigger ageing in peripheral organs, affecting lifespan and quality of life. These mechanisms can have a critical impact on the cardiovascular field. It is well known that ageing is a major predisposing risk factor for coronary syndromes and cardiovascular morbidity and mortality.[4] Hence, growing interest in cardiomyocyte and vascular cell ageing characterized by metabolic remodelling, mitochondrial dysfunction, epigenetic and transcriptomic alterations, and DNA instability.[5] Currently, most therapeutic strategies have been focusing on cardioprotection,[5] immunomodulatory approaches have also been considered. For example, Zacchigna *et al.* have shown that regulatory T cells (Treg) can exert a cardio-tropic paracrine effects in stimulating rodent cardiomyocyte cell division. Treg depletion during gestation was shown to decrease maternal and foetal cardiomyocyte proliferation.[6] Considering that mammalian cardiomyocyte renewal is strictly restrained to the very early postnatal age, with subsequent loss of this programme in the transition towards maturation and adulthood, the regenerative role of Treg in the neonatal heart may offer translational value for future therapeutic strategies. In such a perspective, an anti-ageing approach focused on neutralizing systemic immunosenescence, demonstrated by Yousefzadeh *et al.*, may be of critical value in promoting cardioprotection and cardiomyocyte regeneration.

T cells can also regulate other mechanisms of cardiovascular disease. Pan *et al.* recently demonstrated that aged T cells can accelerate angiotensin II-induced vascular, renal and cardiac oxidative stress, and fibrosis with a crucial mechanism dependent on Interferon (IFN)-γ overproduction. Detrimental cardio-renal effects of the secretome from senescent dysregulated T cells were antagonized by IFN-γ neutralizing antibodies.[7] In this context, therapeutic anti-ageing strategies addressing immune cell senescence and their endogenous DNA reparative mechanisms, may offer a novel approach for preventing accelerated ageing in hypertension.

It has been broadly reported that, in addition to ageing itself, inflammaging can contribute to the onset of vascular stiffness, atherosclerosis, and diabetes.[8] Notably, sustained administration of the mTOR inhibitor rapamycin in diabetic mice following myocardial ischaemia/reperfusion injury has been reported to reduce infarct size, highlighting the STAT3-miR-17-92-mTOR signalling axis as novel cardio-protective candidate target to be exploited in diabetes.[9] Similarly, Yousefzadeh and co-authors reported that rapamycin stimulation in the *Vav-iCre*$^{+/-}$; *Ercc1*$^{-/fl}$ model counteracted immune senescence and ameliorated systemic ageing; thus, senotherapeutics, may represent an appealing option to 'kill two birds with a stone', by (i) specifically tackling immunosenescence-driven disease, while (ii) exerting cardio-protective effects in the elderly and in metabolic syndrome patients at the same time.

Targeting senescence in Vav1+ progenitors may also influence endogenous cardiac reparative mechanisms via resident stromal progenitor cells. Indeed, the murine adult epicardium has been shown to contain injury-responsive clusters of CD45+ Vav1+ haematopoietic resident

*Corresponding author. E-mail: sveva.bollini@unige.it

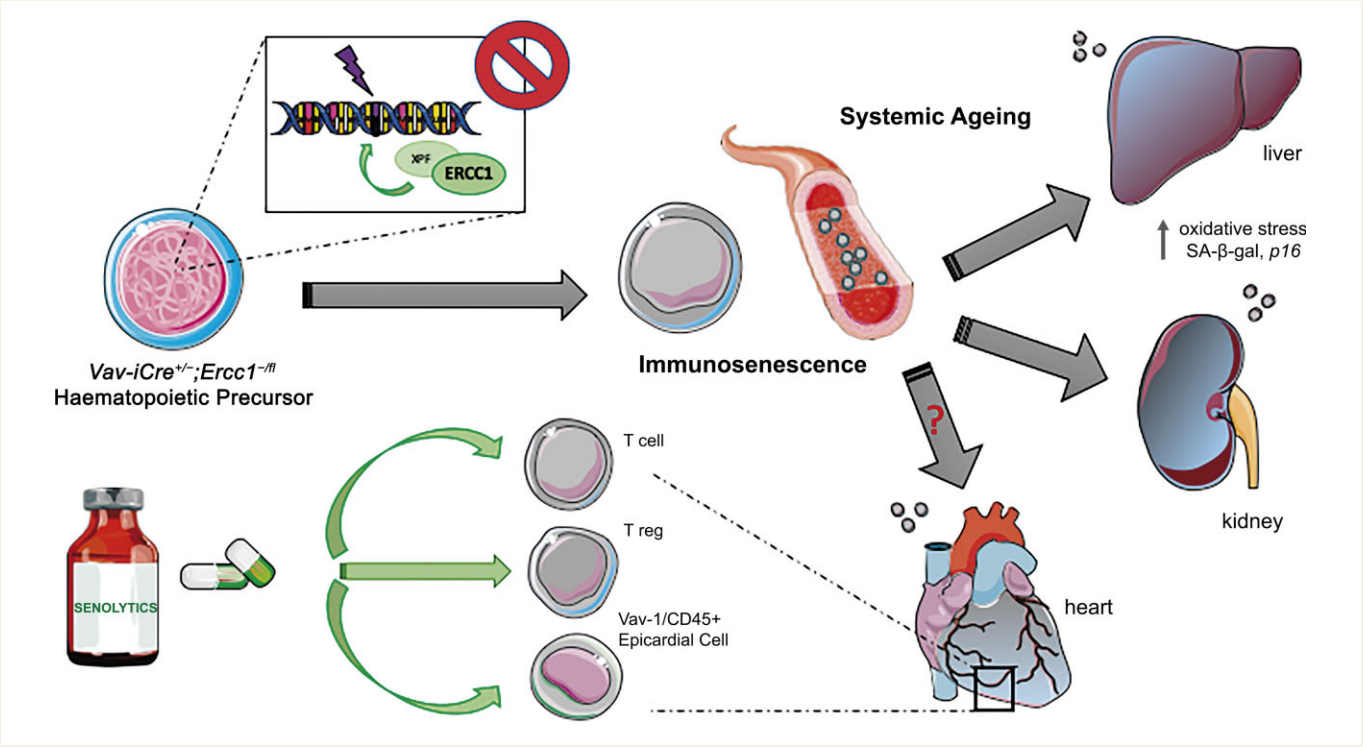

Figure 1 Schematic of *Vav-iCre*$^{+/-}$; *Ercc1*$^{-/fl}$ haematopoietic progenitors in which impaired endogenous DNA repair mechanism and developing immunosenescence in their committed derivatives induces ageing of the solid non-lymphoid peripheral organs (such as liver and kidney) by increased oxidative stress and expression of pro-senescence markers. A putative therapeutic approach targeting immune system and haematopoietic cells with relevant roles in cardiac homeostasis, repair and regeneration can be envisaged. SA-β-gal, senescence-associated β-galactosidase; T cell, T lymphocyte; T reg, regulatory T cell. Schematic has been produced using Smart—Servier Medical Art (https://smart.servier.com).

cells possibly resembling an anatomical niche and contributing during heart embryonic development and adult homeostasis.[10] While bone marrow transplantation studies revealed a supporting role for the haematopoietic compartment in replenishing epicardial CD45+ progenitor turn over, this process was altered by ageing with significant depletion of Vav1+ cells in the cardiac tissue of mature 12–18 months old mice. Given the potential of the adult epicardium to be reactivated and contribute to cardiac repair by secreting paracrine factors, it may be relevant to understand whether such CD45+ stromal component may be pharmacologically targeted by senolytics, as shown in the *Vav-iCre*$^{+/-}$; *Ercc1*$^{-/fl}$ model.

Overall, the study by Yousefzadeh *et al.* sheds new light on systemic ageing being fostered by immunosenescence induced by DNA damage repair impairment in the haematopoietic cell compartment (*Figure 1*). Given the relevance of the immune system and haematopoietic compartment in contributing to cardiovascular homeostasis, repair, and regeneration, the findings provided by this important study could also offer relevant implications for rejuvenating therapies in the cardiovascular system.

Funding

S.B. is funded by 'Curiosity Driven' Starting Grant from University of Genova, Italy.

Conflict of interest: none declared.

References

1. Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, Cui Y, Angelini L, Lee K-A, McGowan SJ, Burrack AL, Wang D, Dong Q, Lu A, Sano T, O'Kelly RD, McGuckian CA, Kato JI, Bank MP, Wade EA, Pillai SPS, Klug J, Ladiges WC, Burd CE, Lewis SE, LaRusso NF, Vo NV, Wang Y, Kelley EE, Huard J, Stromnes IM, Robbins PD, Niedernhofer LJ. An aged immune system drives senescence and ageing of solid organs. *Nature* 2021;**594**:100–105.
2. Kim DE, Dollé MET, Vermeij WP, Gyenis A, Vogel K, Hoeijmakers JHJ, Wiley CD, Davalos AR, Hasty P, Desprez PY, Campisi J. Deficiency in the DNA repair protein ERCC1 triggers a link between senescence and apoptosis in human fibroblasts and mouse skin. *Aging Cell* 2020;**19**:e13072.
3. Robinson AR, Yousefzadeh MJ, Rozgaja TA, Wang J, Li X, Tilstra JS, Feldman CH, Gregg SQ, Johnson CH, Skoda EM, Frantz M-C, Bell-Temin H, Pope-Varsalona H, Gurkar AU, Nasto LA, Robinson RAS, Fuhrmann-Stroissnigg H, Czerwinska J, McGowan SJ, Cantu-Medellin N, Harris JB, Maniar S, Ross MA, Trussoni CE, LaRusso NF, Cifuentes-Pagano E, Pagano PJ, Tudek B, Vo NV, Rigatti LH, Opresko PL, Stolz DB, Watkins SC, Burd CE, Croix CMS, Siuzdak G, Yates NA, Robbins PD, Wang Y, Wipf P, Kelley EE, Niedernhofer LJ. Spontaneous DNA damage to the nuclear genome promotes senescence, redox imbalance and aging. *Redox Biol* 2018;**17**:259–273.
4. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, Alblooshi FMK, Almatrooshi MEAH, Alzaabi MEH, Al Darmaki RS, Lootah SNAH. Global epidemiology of ischemic heart disease: results from the global burden of disease study. *Cureus* 2020;**12**:e9349.
5. Ruiz-Meana M, Bou-Teen D, Ferdinandy P, Gyongyosi M, Pesce M, Perrino C, Schulz R, Sluijter JPG, Tocchetti CG, Thum T, Madonna R. Cardiomyocyte ageing and cardioprotection: consensus document from the ESC working groups cell biology of the heart and myocardial function. *Cardiovasc Res* 2020;**116**:1835–1849.
6. Zacchigna S, Martinelli V, Moimas S, Colliva A, Anzini M, Nordio A, Costa A, Rehman M, Vodret S, Pierro C, Colussi G, Zentilin L, Gutierrez MI, Dirkx E, Long C, Sinagra G, Klatzmann D, Giacca M. Paracrine effect of regulatory T cells promotes cardiomyocyte proliferation during pregnancy and after myocardial infarction. *Nat Commun* 2018;**9**:2432.

7. Pan XX, Wu F, Chen XH, Chen DR, Chen HJ, Kong LR, Ruan CC, Gao PJ. T-cell senescence accelerates angiotensin II-induced target organ damage. *Cardiovasc Res* 2021;**117**:271–283.
8. Yegorov YE, Poznyak AV, Nikiforov NG, Sobenin IA, Orekhov AN. The link between chronic stress and accelerated aging. *Biomedicines* 2020;**8**:198.
9. Samidurai A, Roh SK, Prakash M, Durrant D, Salloum FN, Kukreja RC, Das A. STAT3-miR-17/20 signalling axis plays a critical role in attenuating myocardial infarction following rapamycin treatment in diabetic mice. *Cardiovasc Res* 2020;**116**:2103–2115.
10. Balmer GM, Bollini S, Dubé KN, Martinez-Barbera JP, Williams O, Riley PR. Dynamic haematopoietic cell contribution to the developing and adult epicardium. Nat Commun 2014;**5**:4054.

Authors

Biography: Dr Sveva Bollini graduated in Medical Biotechnology and got her PhD from the University of Padova in Italy, where she studied the cardiomyogenic differentiation potential of human amniotic fluid stem cells with Prof. Paolo De Coppi. During her post-doctoral work, she worked on the lineage characterization of reactivated epicardium-derived progenitor cells for cardiac repair under the supervision of Prof. Paul Riley, at UCL-University College London, London and at the University of Oxford, Oxford in UK. In 2014, she was presented with the 'Rita Levi Montalcini' Young Investigator Award from the Italian Ministry of Research and Education (MIUR) and invited back to Italy to study the paracrine potential of the human amniotic fluid stem cell *secretome* [i.e. the whole of cell-secreted soluble factors and extracellular vesicles (EVs)] to enhance cardiac repair. Currently, she is Group Leader and Associate Professor in Experimental Biology in the Department of Experimental Medicine, University of Genova in Genova, Italy. Her research mainly focuses on the functional characterization of human foetal and perinatal stem cell secretome to unlock endogenous mechanisms of cardiac regeneration following injury and to rejuvenate myocardial renewal. Dr Bollini is a member of the ESC Working Group on Cellular Biology of the Heart (2016) and on Cardiovascular Regenerative and Reparative Medicine (2017). In 2019, she became a member of the Cardiovascular Committee of the International Society for Cell & Gene Therapy and a member of the ESC Scientists of Tomorrow Nucleus.

Biography: Professor Tomasz J. Guzik is the current Editor-in-Chief of Cardiovascular Research. He is the Regius Professor of Physiology and Cardiovascular Pathobiology and an Honorary Consultant Physician in Cardiology at the University of Glasgow. He also serves as a Professor of Medicine at Jagiellonian University Collegium Medicum in Krakow, Poland. Notable recognitions include the honorary Bernard and Joan Marshall Prize in Research Excellence from the BSCR and the prestigious Corcoran Award Lecture at the American Heart Association. He is a recipient of the European Research Council Grant. Professor Guzik's research focuses on vascular biology, hypertension, and clinical immunology.