PERSPECTIVES

Cardiac progenitor cells: old is not always gold

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Translational perspectives

> "Old age isn't so bad when you consider the alternative" – Maurice Chevalier

Ageing causes progressive structural and functional deteriorations of the heart and is a predisposing risk factor for cardiovascular disease (CVD) the major cause of morbidity and mortality in Western countries. An estimated 85.6 million American adults (>1 in 3) have 1 or more types of CVD. Of these, 43.7 million are estimated to be ≥60 years of age (Benjamin *et al.* 2017). Given the increasing incidence and morbidity of heart disease with age, it is of paramount importance to understand fundamental molecular basis of ageing-mediated cardiovascular disease which may lead to the development of both preventive and therapeutic treatments for CVD.

Autologous stem cell therapy offers potential solutions for cardiac repair and regeneration. However, autologous stem cells also present a problem because ageing is primarily associated with stem cell dysfunction. Of different stem cells tested, cardiac resident c-kit$^+$ cardiac progenitors (CPCs) have emerged as one of the promising stem cells for cardiovascular regenerative medicine. There is ample evidence from the literature indicating that transplanted CPCs orchestrate ischaemic tissue repair and regeneration in experimental animals (Gude & Sussman, 2017). Though stem cell therapy appears to be a safe treatment modality for CVD, the therapeutic efficacy observed in clinical trials remains modest (Wang *et al.* 2013). It is largely accepted that low retention and viability, as well as diminished function of transplanted autologous stem cells obtained from aged patients, remain critical unresolved problems that limit the full functional benefits of CPC therapy or any stem cell therapy *per se* for CVD.

Despite the documentation on impaired CPC regenerative capacity with ageing, data on CPC differentiation with ageing is lacking and is the focus of this new study in this issue of *The Journal of Physiology* by Castaldi *et al.* (2017). Here the authors compared CPCs isolated from 3- and 24-month-old c57Bl/6 mice and report that aged CPCs exhibit increased senescence, impaired proliferative capacity and fail to induce cardiac lineage specific genes compared to young CPCs. Furthermore, aged CPCs failed to induce mitochondrial biogenesis or upregulation of oxidative phosphorylation proteins and exhibited impaired paracrine signalling compared to young CPCs. Overall, these findings highlight important differences between young and aged CPCs, which might influence future design of autologous stem cell therapy trials. The current report by Castaldi and colleagues provides important information to the active field of cardiovascular research in outlining how ageing negatively impacts CPCs function. Thus, ageing-mediated CPC dysfunction should be an important parameter to be considered as most of the autologous stem cell therapies are currently tested on elderly patients with CVD. Moreover, many of the potential preclinical interventions have been tested using relatively younger CPCs.

From a *translational perspective*, the study by Castaldi *et al.* suggests new lines of strategies might be needed to augment CPC-based therapies. A comprehensive understanding of molecular mechanisms regulating CPC function in aged CPCs would be highly desirable for development of CPC-based therapy for aged CVD patients. A better understanding of the molecular basis of ageing-induced CPC dysfunction may identify potential target genes whose modulation may rejuvenate old CPCs and improve their functional properties. On similar lines, a recent study showed that neonatal CPCs outperform adult CPCs in functional recovery post-myocardial infarction (Sharma *et al.* 2016), further suggesting that developmental stage affects CPC function. Further, a renewed effort towards studies using allogenic CPCs obtained from younger disease-free subjects would be encouraged. The use of allogenic CPCs could resolve some limitations with autologous CPC transplantation such as tissue harvesting from patients and processing the cells followed by quality control, which takes weeks, delaying the treatment. Importantly, allogenic stem cell therapy could be readily available 'off the shelf' and can be obtained from young and healthy donors, thereby avoiding the issue of CPC dysfunction with advancement of age. However, in this scenario, it would be imperative to first evaluate and resolve potential immune responses/rejection that may be associated with transfer of allogenic CPCs. Alternatively, cell-free components such as CPC-exosomes from allogeneic and healthy, younger CPCs, which are less immunogenic than cells, may be developed as potential therapeutic modality to enhance cardiac repair and regeneration.

References

Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS & Muntner P (2017). Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. *Circulation* **135**, e146–e603.

Castaldi A, Dodia RM, Orogo AM, Zambrano CM, Najor RH, Gustafsson AB, Heller Brown J & Purcell NH (2017). Decline in cellular function of aged mouse c-kit$^+$ cardiac progenitor cells. *J Physiol* **595**, 6249–6262.

Gude NA & Sussman MA (2017). Chasing c-Kit through the heart: taking a broader view. *Pharmacol Res* (in press; https://doi.org/10.1016/j.phrs.2017.06.007).

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Sharma S, Mishra R, Bigham GE, Wehman B, Khan MM, Xu H, Saha P, Goo YA, Datla SR, Chen L, Tulapurkar ME, Taylor BS, Yang P, Karathanasis S, Goodlett DR & Kaushal S (2016). A deep proteome analysis identifies the complete secretome as the functional unit of human cardiac progenitor cells. *Circ Res* **120**, 816–834.

Wang WE, Chen X, Houser SR & Zeng C (2013). Potential of cardiac stem/progenitor cells and induced pluripotent stem cells for cardiac repair in ischaemic heart disease. *Clin Sci* **125**, 319–327.

Additional information

Competing interests

None declared.