Stem cell transplantation

Stem cell therapeutics are emerging as novel alternative treatments for various neurodegenerative diseases based on their regenerative potentials. However, stem cells transplantation might have side effects such as tumor formation that limit their clinical applications. Especially, in vitro expansion of stem cells might provoke genetic instability and tumorigenic potential. To address this issue, Nam et al. analyzed genomic alterations of adult human multipotent neural cells (ahMNCs), a type of human adult neural stem cells, after a long-term in vitro culture process (passage 15) using sensitive analysis techniques including karyotyping, array comparative genomic hybridization (aCGH), and whole-exome sequencing (WES). Although karyotyping did not find any major abnormalities in chromosomal number or structure, diverse copy number variations (CNVs) and genetic mutations were detected by aCGH and WES in all five independent ahMNCs. However, the number of CNVs and genetic mutations did not increase and many of them did not persist as in vitro culture progressed. Although most observed CNVs and genetic mutations were not shared by all five ahMNCs, nonsynonymous missense mutations at MUC4 were found in three out of five long-term cultured ahMNC lines. The genetic instability did not confer in vivo tumorigenic potential to ahMNCs. Collectively, these results indicate that, although genetic instability can be induced by long-term in vitro expansion of stem cells, it is not sufficient to fully exert the tumor formation capacity of stem cells. Other functional effects of such genetic instability need to be further elucidated [1)]

Functional decline of stem cell transplantation in ageing hosts is well documented. The mechanism for this is poorly understood, although it is known that advancing age does not provide an optimal milieu for exogenous stem cells to survive, engraft and differentiate.

Lee et al. showed that n-butylidenephthalide improved human adipose-derived stem cell (hADSC) engraftment via attenuating the production of reactive oxygen species (ROS). It remained unclear whether pre-treated hosts with n-butylidenephthalide can rejuvenate the ageing heart and improve hADSC engraftment by regulating the ROS/NLRP3 inflammasome-mediated cardiac fibrosis after myocardial infarction. One hour after coronary ligation, hADSCs were transplanted into the hearts of young and ageing Wistar rats that were pre-treated with or without n-butylidenephthalide for 3 days. At day 3 after infarction, myocardial infarction was associated with an increase in ROS levels and NLRP3 inflammasome activity with age. hADSC transplant effectively provided a significant decrease in ROS levels, NLRP3 inflammasome activity, IL-1β levels and cardiac fibrosis in either young or old infarcted rats. However, the beneficial effects of hADSCs were greater in young compared with old rats in terms of NLRP3 inflammasome activity. The infarcted ageing rats pre-conditioned by n-butylidenephthalide improved engraftment and differentiation of hADSCs and additionally attenuated cardiac fibrosis compared with hADSCs alone. The anti-inflammation effects of n-butylidenephthalide were reversed by SIN-1. In conclusions, the increased NLRP3 inflammasome activity plays the pathogenesis of ageing-related functional hADSC decline in the ageing hosts. n-butylidenephthalide-pre-treated ageing hosts reversibly ameliorate the harsh microenvironments, improve stem cell engraftment and attenuate cardiac fibrosis after myocardial infarction [2)].

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Nam H, Lee IH, Sa JK, Kim SS, Pyeon HJ, Lee KH, Lee K, Lee SH, Joo KM. Effects of Long-Term In Vitro Expansion on Genetic Stability and Tumor Formation Capacity of Stem Cells. Stem Cell Rev Rep. 2021 Nov 4. doi: 10.1007/s12015-021-10290-z. Epub ahead of print. Erratum in: Stem Cell Rev Rep. 2022 Jan 24;: PMID: 34738209.
2)

Lee TM, Harn HJ, Chiou TW, Chuang MH, Chen CH, Chuang CH, Lin PC, Lin SZ. Host pre-conditioning improves human adipose-derived stem cell transplantation in ageing rats after myocardial infarction: Role of NLRP3 inflammasome. J Cell Mol Med. 2020 Oct 6. doi: 10.1111/jcmm.15403. Epub ahead of print. PMID: 33022900.