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PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

STEM CELLS TRANSLATIONAL MEDICINE

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Significant telomere attrition, DNA damage, oxidative stress, and oncogene expression are among the factors that contribute to the onset of senescence, a cell state associated with cell cycle arrest and a range of phenotypic alterations that impact normal cell function.[1] Given the factors known to induce senescence, many have postulated this mechanism as a protective strategy against malignant transformation. The induction of senescence in stem cells reduces their self-renewal and differentiation capacity and significantly affects their normal function and may impact their therapeutic potential. Indeed, the senescence of stem cells of the hematopoietic system, muscle, brain, skin, and germline during normal aging has been linked to stem cell aging and exhaustion, the loss of stem cell function, and a decline in tissue and organ function.[2] The loss of stemness and proliferative capacity during the ex vivo expansion of stem cells in suboptimal conditions could derive from the induction of senescence-associated pathways; therefore, strategies that interfere with the onset of senescence may extend the therapeutic potential of stem cells undergoing long-term in vitro culture. In our first Featured Article published this month in *STEM CELLS Translational Medicine*, Li et al report how the coinhibition of two signaling pathways during the in vitro expansion of umbilical cord blood-derived CD34-positive cells maintains the stemness of hematopoietic stem cells (HSCs) by inhibiting senescence-associated mechanisms.[3] In a Related article published recently in *STEM CELLS*, Korski et al established how hypoxia boosted the expansion potential and inhibited senescence during the culture of human c-Kit-expressing cardiac progenitor cells (CPCs) derived from heart failure patients.[4]

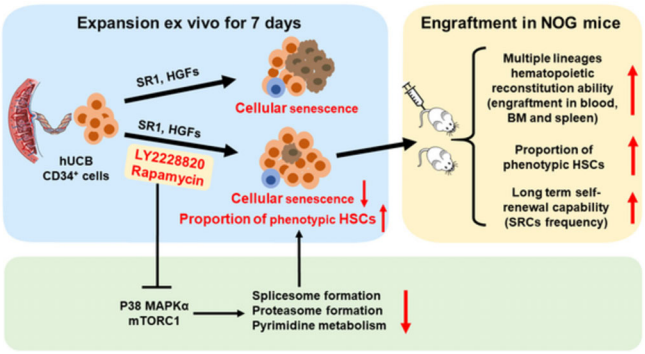
Urinary incontinence, defined as the involuntary loss of urine entailing a social or hygienic problem, represents a common ailment in both males and females. Benign prostatic hyperplasia surgery and radical prostatectomy can prompt the onset of urinary incontinence in male patients.[5] Female stress urinary incontinence, which involves the involuntary leakage of urine during events that result in increased abdominal pressure in the absence of a bladder contraction, also represents a prevalent condition in the female population that impairs quality of life and has a significant socioeconomic impact.[6] Traditional therapeutic options, including pelvic floor rehabilitation, bulking agents, slings, and artificial urinary sphincters, have varying levels of success and are generally accompanied by complications such as high costs and a lack of long-term efficacy. Advanced strategies such as three-dimensional bioprinted muscle or tissue engineering require further development to gain therapeutic relevance; however, stem cell therapies currently have the potential to overcome many of the problems associated with more conventional urinary incontinence treatments.[7] In our second Featured Article published this month in *STEM CELLS Translational Medicine*, Garcia-Arranz et al report on two prospective, nonrandomized phase I/II clinical trials that evaluated the safety and feasibility of autologous adipose mesenchymal stem cell (MSC) transplantation in male and female patients suffering from urinary incontinence.[8] In a Related article published recently in *STEM CELLS*, Yiou et al provided evidence that adipose MSCs can promote the reversal of urinary incontinence and erectile dysfunction associated with radical prostatectomy by secreting paracrine factors and stimulating the host secretome.[9]

FEATURED ARTICLES

Maintaining the stemness of cord blood HSCs by inhibiting senescence

As the senescence of adult stem cells during normal aging has been linked to stem cell exhaustion,[10,11] researchers led by Lingbo Liu (Huazhong University of Science and Technology, Wuhan, China) asked whether the accelerated loss of self-renewing HSCs during the ex vivo expansion of human umbilical cord blood-derived CD34-positive cells could derive from the induction of the senescence program. The early induction of senescence may occur due to the forced hyperproliferation of HSCs in the absence of endogenous niche-associated microenvironmental signaling. In their recent *STEM CELLS Translational Medicine* article,[3] Li et al established that senescence occurred in HSCs undergoing ex vivo expansion in a differentiation-inhibiting growth medium[11] and that senescence onset correlated with the activation of the activated p38 mitogen-activated protein kinase α (p38 MAPKα, p38α) and mammalian target of rapamycin complex 1 (mTORC1) signaling pathways. The authors established that the activation of these pathways compromised the long-term engraftment ability of the HSCs; however, the coinhibition

of both p38α and mTORC1 decreased senescence without increasing apoptosis, maintained the stemness of HSCs during expansion, increased hematopoietic reconstitution ability, and potentiated long-term self-renewal of HSCs. The modulated senescence-associated mechanisms in HSCs included down-regulated spliceosome activity, proteasome formation, and pyrimidine metabolism signaling. Overall, this study's findings suggest that a coinhibition strategy may maintain the stemness of ex vivo expanded HSCs in various culture systems through the inhibition of senescence-associated programs.



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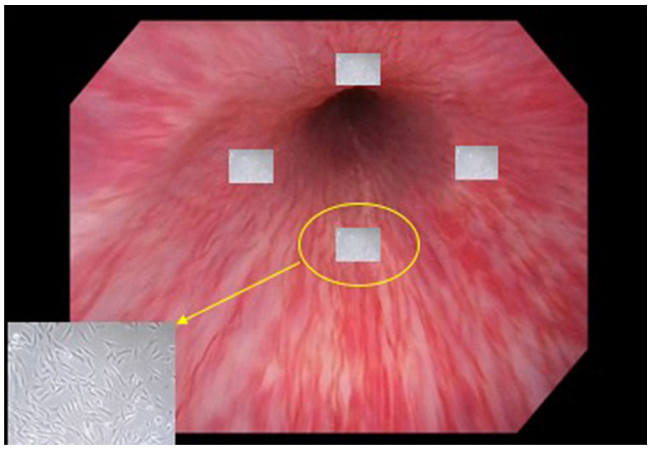
Clinical trials suggest safety and feasibility of MSC therapy for urinary incontinence

Recent studies that evaluated the stromal vascular fraction of adipose tissue and cultured adipose MSCs with bovine collagen[12,13] have underscored the potential for MSCs as an effective treatment for urinary incontinence. In a new *STEM CELLS Translational Medicine* article,[8] researchers from the laboratory of Mariano Garcia-Arranz (Universidad Autónoma de Madrid, Madrid, Spain) reported on their evaluation of the safety and feasibility of endoscopically-administered autologous adipose MSCs in the treatment of urinary incontinence after radical prostatectomy or female stress urinary incontinence in two non-randomized phase I/II clinical trials. Garcia-Arranz et al. isolated autologous adipose MSCs from lipoaspirates to avoid the risk of rejection, transplanted cells following four to six weeks of ex vivo culture, and then evaluated multiple clinical parameters in the 12 months after transplantation. Although the study reported no adverse effects associated with stem cell transplantation, 3 of the 8 male patients and 5 of the 10 female patients exhibited significant improvements, with an objective improvement of greater than 50% and a subjective improvement of 70-80% from baseline. Overall, these exciting findings suggest adipose MSC transplantation as a safe, feasible, and cost-effective means to treat both urinary incontinence after radical prostatectomy and female stress urinary incontinence. In the future, the authors aim to evaluate the effect of increased cell doses to improve efficacy and explore the exact mechanisms controlling therapeutic efficacy.



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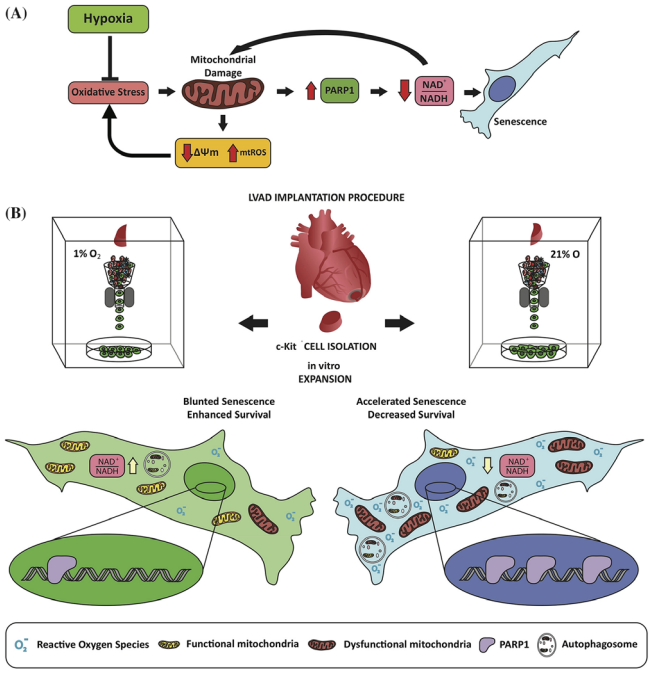
RELATED ARTICLES

Reduced oxidative stress and senescence via hypoxia boosts cardiac progenitor cell potential

Studies have established that the short-term in vitro culture of CPCs under hypoxic conditions can enhance proliferation and migration and improve therapeutic potential[14-16]; however, the differing levels of oxygen tensions and durations of exposure employed had obscured the mechanism involved. In a recent *STEM CELLS* article,[4] researchers led by Mark A. Sussman (San Diego State University, California) reported on the effect of permanent hypoxic conditions (1% oxygen) on human c-Kit-expressing CPCs isolated from left ventricular tissue explants during routine surgery. When compared to cells cultured under normoxic conditions (21% oxygen), Korski et al established that hypoxic conditions supported an increase in the self-renewal capacity of CPCs and inhibited the onset of senescence. Although normoxic conditions increased oxidative stress, prompted a higher susceptibility to apoptosis, and decreased mitochondrial function in CPCs, hypoxic conditions prevented mitochondrial dysfunction, thereby supporting higher oxygen consumption rates and mitochondrial membrane potential. Notably, the inhibition of mitochondrial reactive oxygen species formation in hypoxic conditions, combined with the previously noted benefits, significantly contributed to the observed reduction in CPC senescence. Overall, these findings provided evidence that hypoxia could reduce mitochondrial dysfunction and the production of reactive oxygen species to effectively inhibit oxidative stress in human CPCs and delay the onset of senescence; therefore, hypoxic culture conditions should foster longer-term ex-vivo CPC proliferation and functionality and significantly elevate their therapeutic potential.



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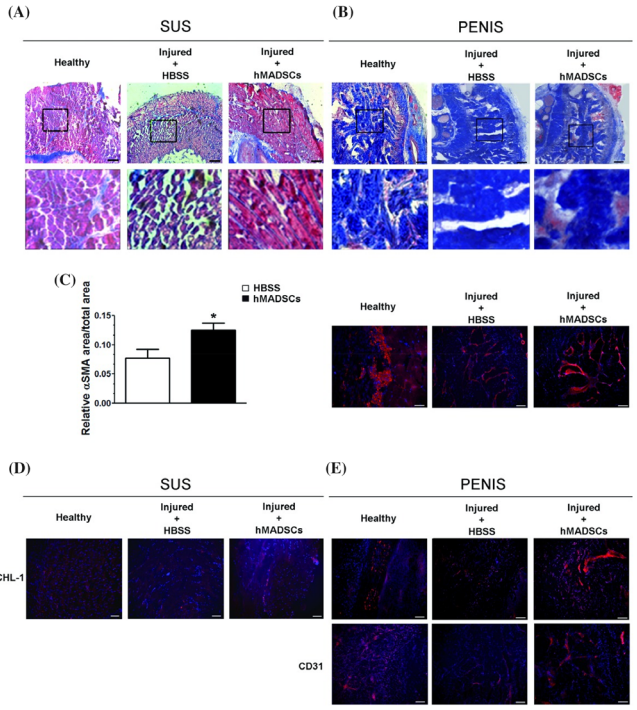
option for radical prostatectomy-associated erectile dysfunction and urinary incontinence in human patients.



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MSC paracrine activity reverses urological dysfunctions associated with radical prostatectomy

Previous research from the laboratories of René Yiou (Henri Mondor Teaching Hospital) and Anne-Marie Rodriguez (Université Paris-Est Créteil, Créteil, France) described the application of adipose MSCs to induce the in vivo repair of dystrophin-deficient skeletal muscle[17] and infarcted myocardium.[18] In a more recent *STEM CELLS* article,[9] the authors tested the therapeutic capacity and mode of function of adipose MSCs in a recently developed immunocompetent rat model that involved the electrocautery of the striated urethral sphincter and penile neurovascular bundles to replicate the damage induced by radical prostatectomy, which can induce erectile dysfunction and urinary incontinence in human male patients.[19] Yiou et al employed noninvasive methods to demonstrate that MSC administration into both the striated urethral sphincter and penis significantly improved the incidence of urinary continence and erectile function in rats; however, the regenerative effects observed after MSC administration did not derive from transdifferentiation nor robust engraftment at the injection sites, and so, likely derived from a paracrine process involving the secretion of multiple regenerative, reparative, and anti-inflammatory factors by MSCs and the stimulation of the host's secretome. In this dual paracrine process, potential effectors included vascular endothelial growth factor and hepatocyte growth factor, which are both known to promote angiogenesis, cell survival, and the recruitment of MSCs to injury sites. Overall, these fascinating findings provide the foundation for the implementation of adipose MSCs as a treatment

REFERENCES

1. Herranz N, Gil J. Mechanisms and functions of cellular senescence. *J Clin Invest*. 2018;128:1238-1246.
2. Schultz MB, Sinclair DA. When stem cells grow old: phenotypes and mechanisms of stem cell aging. *Development*. 2016;143:3-14.
3. Li X, Ma X, Chen Y, et al. Coinhibition of activated p38 MAPKα and mTORC1 potentiates stemness maintenance of HSCs from SR1-expanded human cord blood CD34+ cells via inhibition of senescence. *Stem Cells Translational Medicine*. 2020;9.
4. Korski KI, Kubli DA, Wang BJ, et al. Hypoxia prevents mitochondrial dysfunction and senescence in human c-Kit+ cardiac progenitor cells. *Stem Cells*. 2019;37:555-567.
5. Nam Robert K, Herschorn S, Loblaw DA, et al. Population based study of long-term rates of surgery for urinary incontinence after radical prostatectomy for prostate cancer. *J Urol*. 2012;188:502-506.
6. Capobianco G, Madonia M, Morelli S, et al. Management of female stress urinary incontinence: a care pathway and update. *Maturitas*. 2018;109:32-38.
7. Lin C-S, Lue TF. Stem cell therapy for stress urinary incontinence: a critical review. *Stem Cells Dev*. 2012;21:834-843.
8. Garcia-Arranz M, Alonso-Gregorio S, Fontana-Portella P, et al. Two phase I/II clinical trials for the treatment of urinary incontinence with autologous mesenchymal stem cells. *Stem Cells Translational Medicine*. 2020;9.
9. Yiou R, Mahrouf-Yorgov M, Trébeau C, et al. Delivery of human mesenchymal adipose-derived stem cells restores multiple urological dysfunctions in a rat model mimicking radical prostatectomy damages through tissue-specific paracrine mechanisms. *Stem Cells*. 2016;34:392-404.

10. Wahlster L, Daley GQ. Progress towards generation of human haematopoietic stem cells. *Nat Cell Biol*. 2016;18:1111-1117.
11. Boitano AE, Wang J, Romeo R, et al. Aryl hydrocarbon receptor antagonists promote the expansion of human hematopoietic stem cells. *Science*. 2010;329:1345-1348.
12. Gotoh M, Yamamoto T, Kato M, et al. Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients. *Int J Urol*. 2014;21:294-300.
13. Kuismanen K, Sartoneva R, Haimi S, et al. Autologous adipose stem cells in treatment of female stress urinary incontinence: results of a pilot study. *Stem Cells Translational Medicine*. 2014;3:936-941.
14. Bellio MA, Rodrigues CO, Landin AM, et al. Physiological and hypoxic oxygen concentration differentially regulates human c-Kit+ cardiac stem cell proliferation and migration. *Am J Physiol Heart Circ Physiol*. 2016;311:H1509-H1519.
15. Tang YL, Zhu W, Cheng M, et al. Hypoxic preconditioning enhances the benefit of cardiac progenitor cell therapy for treatment of myocardial infarction by inducing CXCR4 expression. *Circ Res*. 2009;104:1209-1216.
16. Xu R, Sun Y, Chen Z, Yao Y, Genshan M. Hypoxic preconditioning inhibits hypoxia-induced apoptosis of cardiac progenitor cells via the PI3K/Akt-DNMT1-p53 pathway. *Sci Rep*. 2016;6:30922.
17. Rodriguez A-M, Pisani D, Dechesne CA, et al. Transplantation of a multipotent cell population from human adipose tissue induces dystrophin expression in the immunocompetent mdx mouse. *J Exp Med*. 2005;201:1397-1405.
18. Figeac F, Lesault P-F, Le Coz O, et al. Nanotubular crosstalk with distressed cardiomyocytes stimulates the paracrine repair function of mesenchymal stem cells. *Stem Cells*. 2014;32:216-230.
19. Khodari M, Souktani R, Le Coz O, et al. Monitoring of erectile and urethral sphincter dysfunctions in a rat model mimicking radical prostatectomy damage. *J Sex Med*. 2012;9:2827-2837.