Stem Cells, 2023, **41**, 307–309
https://doi.org/10.1093/stmcls/sxad011
Editorial

Advances in Stem Cell Immunotherapy

Johnathon D. Anderson*

Department of Otolaryngology, University of California Davis School of Medicine, Sacramento, CA, USA
*Corresponding author: Email: joanderson@ucdavis.edu

The idea of exploiting the host's immune system to treat disease dates back to the Ebers Papyrus of ancient Egypt.[1] Immunotherapy relies on the insight that the immune system plays an essential role in many diseases. In recent decades, a large body of work from across the globe has advanced numerous immunotherapies into clinical practice, from cancer to multiple sclerosis. This past year *STEM CELLS* has been at the forefront of this field through publishing numerous papers that have further advanced this exciting field.

Mesenchymal stromal cells (MSCs) were first identified in the bone marrow by Tavassoli and Crosby in the 1960s,[2] with the term "MSC" first being coined by Kaplan in 1991.[3] In the years since, MSC-like cells have been found in multiple tissue compartments throughout the body. They are well characterized for their immunoregulatory properties in various disease models and clinical trials.[4]

Recently, Na Song from Khalid Shah's laboratory published a rigorous review of the literature and clinical findings surrounding the application of MSCs in severe cases of COVID.[5] These findings indicate that MSCs have the potential to attenuate the cytokine storm that occurs in patients with severe cases of COVID. They also outline several clinical trials that are currently underway which employ MSC to treat COVID (NCT04313322, NCT04428801, NCT04336254).

Another exciting area of research exploring MSCs as immunotherapy is in the realm of type 2 diabetes mellitus. Chen et al recently published a fantastic review of this growing body of research, including an examination of MSC-derived extracellular vesicles, sometimes referred to as exosomes.[6] In this review, the authors outline the underlying mechanisms of MSC-mediated immune modulation, focusing on their paracrine effects. They also provide an excellent summary of the current preclinical and clinical investigations of MSC-based therapies for T2DM.

Recessive dystrophic epidermolysis bullosa (RDEB) is a disease in which the skin barrier is disrupted and often presents with blistering of the skin. RDEB is a monogenetic disease that results from biallelic mutations in the COL7A1 gene encoding for type VII collagen. Riedl et al recently published their work in *STEM CELLS* which demonstrates *Hox* genes are differentially expressed in RDEB.[7] These *Hox* genes, including *HOXA3*, alter the migratory and skin homing properties of a dermal-derived population of MSCs (DSCs), which are positive for ABCB5 (ABCB5+ DSCs). This work includes an examination of MSCs immunomodulatory effects on macrophages.

T and B cells are 2 key populations that mediate key lymphocyte activation components. Recently, Zidan et al published their work in *STEM CELLS*, demonstrating that urinary-derived MSCs (USCs) suppress the proliferation of T and B cells that have been activated via anti-CD3/CD28.[8] However, interestingly, USCs increased the proliferation and antibody secretion of resting B cells. The authors note that this intrinsic B-cell stimulatory capacity of USCs opens up new possibilities for their therapeutic use in conditions where B cells activation is required, for example, cancer immunotherapy.

Radiotherapy (RT) is still a standard cancer treatment, with around half of solid-tumor cancer patients being irradiated in the course of their disease.[9-11] RT has immunological effects reshaping the tumor microenvironment, but often fails to elicit potent anti-tumor immune responses as these effects can be immunostimulatory and immunosuppressive. Cancer stem cells (CSCs) are a vital cellular population in this regard. CSCs can be resistant to RT therapy. Rückert et al recently published an excellent review of this exciting area of research.[9] The authors propose combining RT with other treatments such as hyperthermia or immunotherapy might be necessary to eradicate these radioresistant CSCs. The authors also discuss numerous clinical trials involving the combination of RT with immunotherapy.[12-14]

Received: 29 July 2022; Accepted: 9 January 2023.

PD-L1 is an immune checkpoint receptor that plays a crucial role in many cancers' ability to regulate immune activation within the tumor microenvironment negatively. The immunosuppressive properties of immune checkpoint proteins such as PD-L1 are critical to tumor progression. Kou et al demonstrate that the expression of PD-L1 increases as stem cells differentiate and lung cancer cells lose their plasticity.[15] They also report that TGF-β induces PD-L1 expression and concurrently reduces the expression of one of the key stem cell and plasticity genes, SOX2.

In certain types of cancer, tumors may regress after allogeneic hematopoietic stem cell transplantation (HSCT), when donor lymphocytes attack the tumor. This phenomenon is referred to as the graft-versus-tumor effect (GVT). Unfortunately, GVT is frequently limited by poor specificity or the low frequency of tumor-specific lymphocytes, resulting in an incomplete and unsustained anti-tumor response. Barisic and Childs published a review of the preclinical and clinical research in this area.[16] The review focuses on the lessons learned from clinical trials, which hold potential for creating more tumor-specific immunotherapies, which may allow for greater efficacy and enhanced safety profile.[17-25]

Toll-like receptors (TLRs) regulate the crosstalk between the adaptive and innate immune systems. TLRs interact with endogenous molecules such as damage-associated molecular patterns (DAMPs), which are generated during tissue injury. TLRs have also been found to be expressed on numerous stem cell and progenitor populations, which allows them to sense tissue injury. Seong et al report that TLR5 is upregulated in neural stem cells (NSCs) and embryonic stem cells.[26] The authors report that TLR5 is a positive regulator of neural differentiation in ESCs and NSCs. Neurogenesis has been implicated in learning and memory performance. The authors investigate the relationship between TLR5-induced neurogenesis and memory, by performing various memory tests using TLR5 KO mice. Their results suggest that TLR5 enhances fear memory performance associated with TLR5-induced hippocampal neurogenesis in mice, while basal locomotor activity was not altered. This work suggests that TLR5 is an essential mediator of neurogenesis from NSCs in mice and potentially represents a novel therapeutic target in neurological disorders.

The immunotherapy papers published in *STEM CELLS* focus on a diverse set of stem cell populations including HSCs, NSCs, ESCs, USCs, DSCs, and MSCs derived from numerous tissue compartments. This exciting work also spans an impressive array of diseases and therapeutic approaches. I truly look forward to seeing the next developments in this field, especially in the realm of stem cell-based therapies.

To read the articles in the Immunotherapy Collection, go to https://academic.oup.com/stmcls/pages/immunotherapy

Conflict of Interest

The author declared no potential conflicts of interest.

References

1. Radha G, Lopus M. The spontaneous remission of cancer: Current insights and therapeutic significance. *Transl Oncol*. 2021;14:101166. https://doi.org/10.1016/j.tranon.2021.101166
2. Tavassoli M, Crosby WH. Transplantation of marrow to extramedullary sites. *Science*. 1968;161:54-56. https://doi.org/10.1126/science.161.3836.54
3. Caplan AI. Mesenchymal stem cells. *J Orthop Res*. 1991;9:641-650. https://doi.org/10.1002/jor.1100090504
4. Galipeau J, Sensebe L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell*. 2018;22:824-833. https://doi.org/10.1016/j.stem.2018.05.004
5. Song N, et al. Mesenchymal stem cell immunomodulation: In pursuit of controlling COVID-19 related cytokine storm. *Stem Cells*. 2021;39:707-722. https://doi.org/10.1002/stem.3354
6. Chen J, Zheng CX, JinY, Hu CH. Mesenchymal stromal cell-mediated immune regulation: a promising remedy in the therapy of type 2 diabetes mellitus. *Stem Cells*. 2021;39:838-852. 10.1002/stem.3357
7. Riedl J, et al. ABCB5+ dermal mesenchymal stromal cells with favorable skin homing and local immunomodulation for recessive dystrophic epidermolysis bullosa treatment. *Stem Cells*. 2021;39:897-903. https://doi.org/10.1002/stem.3356
8. Zidan AA, et al. Urine stem cells are equipped to provide B cell survival signals. *Stem Cells*. 2021;39:803-818. https://doi.org/10.1002/stem.3351
9. Ruckert M, Flohr AS, Hecht M, Gaipl US. Radiotherapy and the immune system: More than just immune suppression. *Stem Cells*. 2021:39:1155-1165. https://doi.org/10.1002/stem.3391
10. Tyldesley S, et al. Estimating the need for radiotherapy for patients with prostate, breast, and lung cancers: verification of model estimates of need with radiotherapy utilization data from British Columbia. *Int J Radiat Oncol Biol Phys*. 2011;79:1507-1515. https://doi.org/10.1016/j.ijrobp.2009.12.070
11. Barton MB, et al. Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. *Radiother Oncol*. 2014;112:140-144. https://doi.org/10.1016/j.radonc.2014.03.024
12. Hecht M, et al. Safety and efficacy of single cycle induction treatment with cisplatin/docetaxel/ durvalumab/tremelimumab in locally advanced HNSCC: first results of CheckRad-CD8. *J Immunother Cancer*. 2020;8. https://doi.org/10.1136/jitc-2020-001378
13. Xing D, Siva S, Hanna GG. The Abscopal Effect of stereotactic radiotherapy and immunotherapy: Fool's Gold or El Dorado? *Clin Oncol (R Coll Radiol)*. 2019;31:432-443. https://doi.org/10.1016/j.clon.2019.04.006
14. Arina A, Gutiontov SI, Weichselbaum RR. Radiotherapy and immunotherapy for cancer: from "Systemic" to "Multisite". *Clin Cancer Res*. 2020;26:2777-2782. https://doi.org/10.1158/1078-0432.CCR-19-2034
15. Kuo MH, et al. Cytokine and epigenetic regulation of programmed death-ligand 1 in stem cell differentiation and cancer cell plasticity. *Stem Cells*. 2021;39:1298-1309. https://doi.org/10.1002/stem.3429
16. Barisic S, Childs RW. Graft-versus-solid-tumor effect: from hematopoietic stem cell transplantation to adoptive cell therapies. *Stem Cells*. 2022;40:556-563. https://doi.org/10.1093/stmcls/sxac021
17. Takahashi Y, et al. Regression of human kidney cancer following allogeneic stem cell transplantation is associated with recognition of an HERV-E antigen by T cells. *J Clin Invest*. 2008;118:1099-1109. https://doi.org/10.1172/JCI34409
18. Barkholt L, et al. Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe. *Ann Oncol*. 2006;17:1134-1140. https://doi.org/10.1093/annonc/mdl086
19. Artz AS, et al. Long-term follow-up of nonmyeloablative allogeneic stem cell transplantation for renal cell carcinoma: The University of Chicago Experience. *Bone Marrow Transplant*. 2005;35:253-260. https://doi.org/10.1038/sj.bmt.1704760
20. Ueno NT, et al. Rapid induction of complete donor chimerism by the use of a reduced-intensity conditioning regimen composed of fludarabine and melphalan in allogeneic stem cell transplantation for metastatic solid tumors. *Blood*. 2003;102:3829-3836. https://doi.org/10.1182/blood-2003-04-1022

21. Hentschke P, et al. Low-intensity conditioning and hematopoietic stem cell transplantation in patients with renal and colon carcinoma. *Bone Marrow Transplant*. 2003;31:253-261. https://doi.org/10.1038/sj.bmt.1703811
22. Rini BI, Zimmerman T, Stadler WM, Gajewski TF, Vogelzang NJ. Allogeneic stem-cell transplantation of renal cell cancer after nonmyeloablative chemotherapy: feasibility, engraftment, and clinical results. *J Clin Oncol*. 2002;20:2017-2024. https://doi.org/10.1200/JCO.2002.08.068
23. Childs R, et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *N Engl J Med*. 2000;343:750-758. https://doi.org/10.1056/NEJM200009143431101
24. Bregni M, et al. Nonmyeloablative conditioning followed by hematopoietic cell allografting and donor lymphocyte infusions for patients with metastatic renal and breast cancer. *Blood*. 2002;99:4234-4236. https://doi.org/10.1182/blood.v99.11.4234
25. Pedrazzoli P, et al. Allogeneic blood stem cell transplantation after a reduced-intensity, preparative regimen: a pilot study in patients with refractory malignancies. *Cancer*. 2002;94:2409-2415. https://doi.org/10.1002/cncr.10491
26. Seong KJ, et al. Toll-like receptor 5 promotes the neurogenesis from embryonic stem cells and adult hippocampal neural stem cells in mice. *Stem Cells*. 2022;40:303-317. https://doi.org/10.1093/stmcls/sxab025