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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.

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Regulatory T cells, or Tregs, regulate immune responses, maintain tolerance to self-antigens, and prevent autoimmune disease by suppressing/downregulating the activation, proliferation, and cytokine production of immune cells such as CD4+/CD8+ T cells, B-Lymphocytes, dendritic cells, monocytes, and granulocytes.[1] Tregs influence the function of said immune cells through direct mechanisms, such as the secretion of cytokines or the production of enzymes such as granzyme and perforin, and indirect mechanisms, which include alterations to the immune cell microenvironment. Studies have highlighted Treg dysfunction in immune-related pathologies such as graft vs. host disease and multiple sclerosis[2,3]; meanwhile, other preclinical research has underscored the therapeutic potential of Treg modulation in conditions such as autoimmune disease, cancer, and wound healing. Furthermore, the administration of Tregs has been explored as a means to facilitate successful organ transplantation by inducing immunotolerance. To this end, multiple clinical trials are currently evaluating Treg therapy in several disease states. In our first Feature Article published this month in *STEM CELLS Translational Medicine*, Caplan et al. describe how treatment with human Tregs expanded from umbilical cord blood can modulate the central and peripheral immune responses in a rodent model of traumatic brain injury (TBI) and may improve patient outcomes.[4] In a Related Article published recently in *STEM CELLS*, Li et al. demonstrated that transplanted human induced pluripotent stem cell-derived mesenchymal stem cells (iPSCs-MSCs) displayed an immunosuppressive effect in a host vs. graft reaction mouse model through the inhibition of caspase cleavage by secreted factors and an associated upregulation of Tregs.[5]

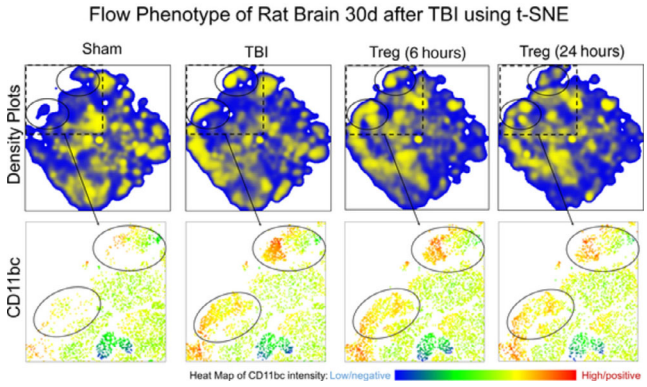
The approximately five million hair follicles present in the human body vary in size and shape according to their location, and while no new follicles form after birth, the size of the follicles and hairs continues to change over time. The cells of the hair follicles resident in the dermal layer of mammalian skin regulate hair growth via complex interactions with hormones, neuropeptides, and immune cells. Each hair follicle comprises a lower, middle, and upper segment, with the lower segment undergoing repeated cycles of regression (catagen), resting (telogen), and growth (anagen) phases under the control of bulge-resident hair follicle stem cells (HFSCs). The dysregulation of the hair follicle growth cycle can prompt hair loss, and while this condition is not life-threatening, it can induce low self-esteem and psychological distress in patients.[6] Therefore, many have sought to develop safe and effective therapeutic options for hair loss,[7] and ongoing complementary studies have sought to fully define the molecular mechanisms controlling the hair follicle cycle to potentially guide the development novel treatment strategies. In our second Feature Article published this month in *STEM CELLS Translational Medicine*, Tak et al. report that a topical solution of adipose stem cell (ASC) constituent extract may represent a safe and effective means to induce hair regrowth in androgenetic alopecia patients by increasing both hair density and thickness.[8] In a Related Article published recently in *STEM CELLS*, Suen et al. demonstrated that Hes1, a major Notch downstream transcriptional repressor, reinforces Hedgehog signaling to expand and replenish HSFCs to maintain hair cycle homeostasis.[9]

FEATURED ARTICLES

Cord Blood Tregs Can Improve Brain Injury Outcomes by Modulating Immune Responses

Researchers led by Scott D. Olson and Charles S. Cox Jr. (University of Texas Health Science Center at Houston, USA) previously established that both MSCs and multipotent adult progenitor cells could dampen microglial activation and polarize them into a pro-reparative, anti-inflammatory phenotype that improved outcomes in preclinical models[10,11] through a mechanism involving Treg modulation.[12] Based on these findings, the team evaluated the ability of human Tregs derived from cord blood to directly modulate the immune response and improve outcomes following TBI and reported their findings in a recent *STEM CELLS Translational Medicine* article.[4] Beginning with in vitro analysis employing human and rat immune cells, Caplan et al. established that umbilical cord Tregs robustly inhibited the production of proinflammatory cytokines such as Interferon (INF)-γ from peripheral blood mononuclear cells, tumor necrosis factor (TNF)-α and IFN-γ from splenocytes, and TNF-α from activated microglia. Subsequent in vivo analysis in a rat TBI model established that the administration of umbilical cord Tregs modulated the

peripheral and central immune responses at time points significant for subacute and chronic injury. Furthermore, Tregs significantly inhibited microgliosis in the injured hemisphere of the brain, indicating their ability to suppress the chronic secondary neuroinflammation that contributes to ongoing brain injury and long-term morbidity. The authors note that recent improvements to isolation and expansion techniques may now permit the evaluation of autologous and non-autologous Tregs in clinical trials as a cell therapy for TBI.



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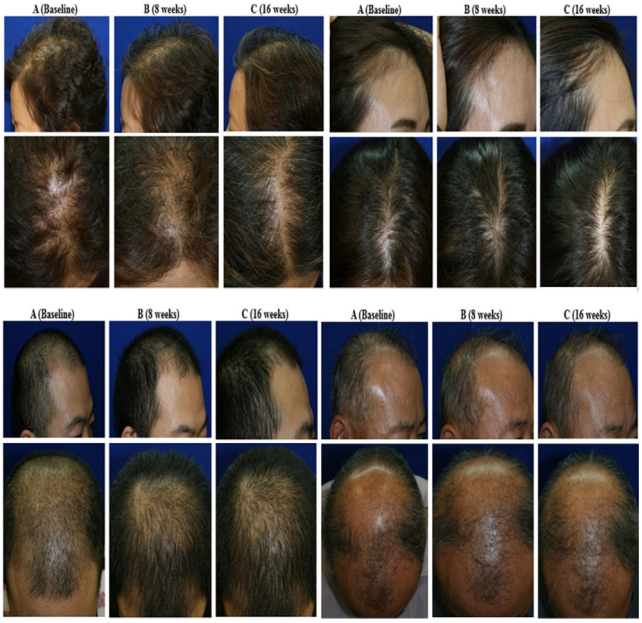
Adipose Stem Cells: A Safe and Effective Means to Reverse Alopecia-Associated Hair Loss

Treatments for androgenetic alopecia, a common type of hair loss, carry the risk of detrimental side-effects[13]; therefore, many have sought to develop novel, safer therapeutic options. Retrospective human studies reported that ASCs promoted hair growth in alopecia patients,[14,15] and these findings prompted researchers from the laboratories of Sang Yeoup Lee and A. Ra Cho (Pusan National University Yangsan Hospital, Yangsan, South Korea) to undertake a randomized, double-blind, vehicle-controlled clinical trial in middle-aged androgenetic alopecia patients to evaluate the topical application of ASC constituent extract. Reporting in *STEM CELLS Translational Medicine*,[8] Tak et al. assessed the effects of twice-daily self-application of ASC constituent extract over 16 weeks on hair count and thickness. Overall, ASC constituent extract induced a significant increase in hair count between 8 and 16 weeks when compared to the vehicle control patients, while the authors also noted a significant improvement in hair diameter after 16 weeks. Importantly, the study noted the tolerability of ASC constituent extract treatment, with no toxicities or severe adverse effects observed. Together, these data support the topical application of ASC constituent extract as an alternative therapeutic strategy for hair regrowth in androgenetic alopecia patients. The team behind these fascinating findings now hopes to evaluate the longer-term effects in a multicenter trial with an increased number of patients and to assess the amount of trial product reaching the hair follicles.



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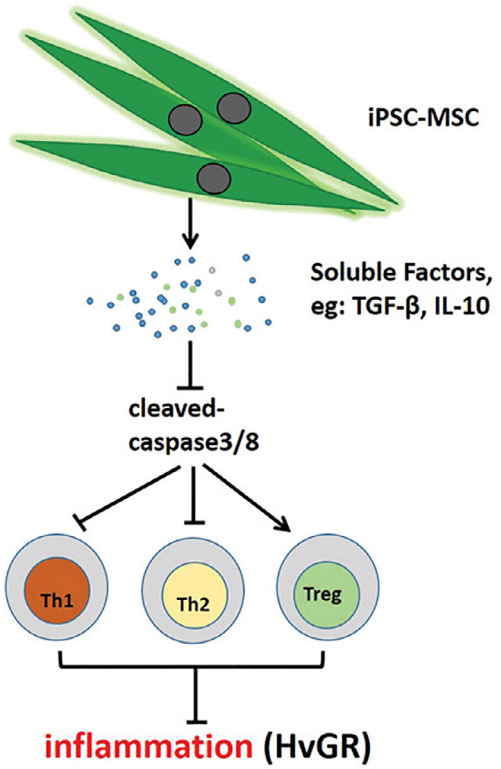
RELATED ARTICLES

iPSC-MSCs Suppress T Cell Responses by Inhibiting Caspase Cleavage

Researchers from the laboratories of Qing-Ling Fu (Sun Yat-sen University, Guangzhou) and Zhongquan Qi (Xiamen University, Fujian, China) previously reported that iPSCs-MSCs possessed improved characteristics related to their therapeutic potential when compared with bone marrow MSCs.[16] Additionbally, the team assessed the impact of iPSC-MSCs on distinct T cell populations in the hope of employing them to facilitate cell and tissue transplantation.[17] In their recent *STEM CELLS* article, the authors reported on a study of the immunomodulatory properties of iPSC-MSCs regarding T cell responses in vivo in a host vs. graft reaction (HvGR) model.[5] Li et al. demonstrated that iPSC-MSC transplantation associated with higher cell survival and lower inflammatory cell infiltration; furthermore, transplanted iPSC-MSCs inhibited T cell proliferation and T helper (Th) 1/2 responses and upregulated Th17 and Treg subsets. Interestingly, the team linked these iPSC-MSC-driven effects to the inhibited cleavage of caspases 3 and 8 in T cells. Subsequent analysis of the soluble factors secreted by iPSC-MSCs highlighted the importance of transforming growth factor (TGF)-beta11/2/3, interleukin(IL)-10, and monocyte chemoattractant protein-1 in this mechanism, which was corroborated by the observation of a similar T cell response to the administration of soluble factors to that elicited from iPSC-MSC transplantation. Overall, these findings support the inhibition of caspase cleavage induced by paracrine acting factors as a novel

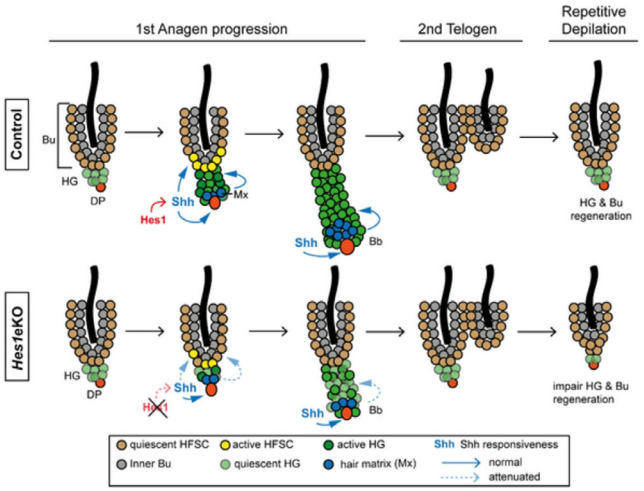
immunomodulatory mechanism controlling the impact of iPSC-MSCs on T cell responses, including Tregs.



https://doi.org/10.1002/stem.2638

Hes1 Potentiates Hedgehog Signaling to Maintain Hair Cycle Homeostasis

Researchers led by Liang-Tung Yang (National Health Research Institutes, Miaoli County, Taiwan) previously established that the ablation of a critical Notch signaling component in hair follicle lineages resulted in the disruption of the transition from rest phase to the growth phase, which is normally maintained by HFSCs.[18] In their recent *STEM CELLS* study, the team sought to explore the role of Hes1, a Notch downstream transcriptional repressor,[19] in hair growth initiation and HFSC maintenance during the hair cycle.[9] Suen et al. discovered that the deletion of Hes1 in the epithelium retarded hair growth even though the hair cycle progressed normally. Analysis in wild type mice revealed the upregulation of Hes1 in the lower bulge and hair germ during growth phase initiation; however, the loss of Hes1 delayed the activation of the secondary hair germ, a source of HSFCs, prompted a shortened anagen phase, and caused reduced hair shaft length, although the team observed no alterations to follicular lineage identity. Furthermore, Hes1 loss also prompted impaired hair regeneration upon repetitive depilation. To discover the mechanisms involved, the authors employed microarray gene profiling of HFSCs, discovering that Hes1 functions to modulate sonic hedgehog responsiveness during the initiation of the growth phase to mediate the expansion of the hair germ and the replenishment of the HFSCs to maintain hair cycle homeostasis. Overall, this study provided a deeper understanding of progenitor activation and stem cell maintenance during the hair cycle.



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