OPEN ACCESS Freely available online

Journal of Cell Science & Therapy

Short Communication

Strategies for the Hair Follicle Regeneration: Extracellular Vesicles as a Novel Therapeutic Biomolecule

Chang Hoon Seo*

New Drug Development Center, Daegu-Gyeongbuk Medical Innovation Foundation (K-MEDI hub), Daegu, Republic of Korea

DESCRIPTION

Hair follicle (HF) regeneration can be understood generally in two perspectives. One is *de novo* synthesis (neogenesis) of hair follicles and another is the promotion of hair follicle growth, which means facilitating the hair cycle transition from telogen (resting phase) to anagen (active phase). Recently, some notable studies applying Extracellular Vesicles (EVs) to both HF neogenesis and the promotion of HF growth have been reported implying the possibility to overcome the shortages of current hair loss therapies [1]. This paper, in two perspectives mentioned above, explores the attempts for the hair follicle regeneration.

De novo synthesis (neogenesis) of hair follicles

The strategy for neogenesis can be designed by considering the developmental process of HFs as a skin appendage. Initial hair induction relies on dermal-epidermal interactions which causes dermal placode formation, and subsequently differentiations into dermal papilla. Dermal Papilla (DP) then achieves the hair-inductive potency (trichogenecity) to create a hair shaft by the active crosstalk with adjacent epidermal microenvironment. Therefore, in order to realize hair follicle neogenesis, acquisition of hair-inductive (trichogenic) DP cells is an overarching concern. Various approaches to address the concern have been tried such as supplementation of necessary factors (keratinocyte conditioned medium, or activators of Wnt/β-catenin) to DP cells and the application of three-Dimensional (3D) spheroid culture to DP cells [2]. Spheroid formation of human DP cells actually makes them more representative of the intact in vivo DPs regarding to trichogenicity [3,4]. In addition, necessary genes and molecular signallings of 3D cultured DP spheres (3D-DPs) involved in hair follicle neogenesis have been investigated for enhancing the trichogenicity of 3D-DPs or discovering any clues to find any alternatives to them [5-7].

Inspired by the significance of 3D-DPs, the effect of EVs derived from 3D-DPs (3D-DPs-EVs) on hair follicle neogenesis has been evaluated. When 3D-DPs-EVs were additionally treated to cultured 3D-DPs, the number of induced hair formation was increased by 2-folds compared to that of control 3D-DPs [8]. This study has brought up a topic about the autocrine effect mediated by EVs while DP cells were 3D cultured. Considering that DP cells are a type of adult mesenchymal stem cells, Seo, et al. evaluated human Adipose Derived Mesenchymal Stem Cells (ADSCs) as Three-Dimensional (3D) spheroid forms to replace the trichogenic 3D-DPs [9]. However, 3D-ADSCs were found not to be a promising option as trichogenic dermal components as they showed poor capability to induce human HF formation. A study has been very recently reported on the application of EVs derived from mouse ADSCs (mADSCs- EVs). Wu, et al. showed that mADSCs- EVs are capable to enhance mouse HF neogenesis by the induction of Platelet Derived Growth Factor (PDGF) and vascular endothelial growth factor (VEGF) [10].

The promotion of hair growth

Hu, et al. have recently revealed that the treatment of 3D-DPs is more effective to promote hair growth than 5% minoxidil (widely used as a positive control for hair growth) [11]. They have further elucidated that the growth promotion effect can be achieved by 3D-DPs-EVs only, instead of 3D-DPs, and the effect is attributed to micRNA-218-4p in the EVs acting as an activator of β-catenin signalling [11]. Dermal Fibroblasts (DFs) are one of dermal cell populations. Transfecting DFs with essential factors and treatment of growth factors to DFs have been tried to transfer their characteristics similar to DP cells. Riche, et al. found that EVs derived from the DFs stimulated hair growth and the stimulatory effect was more strengthened when DFs were pre-treated with both Basic Fibroblast Growth Factor (bFGF) and PDGF [12]. In accordance with another study on the use of Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSC), EVs derived from BM-MSC have a potential to augment both DP cells' activity and hair cycle progression from telogen to anagen [13].

It is reported that perifollicular macrophages promoted hair growth, thereafter which was through TNF-induced AKT/β-catenin signalling in Lgr5+ HF stem cells [14,15]. Inspired by the

Correspondence to: Chang Hoon Seo, New Drug Development Center, Daegu-Gyeongbuk Medical Innovation Foundation (K-MEDI hub), Daegu, Republic of Korea, E-mail: schch84@kmedihub.re.kr

Received: 14-Apr-2022, Manuscript No. JCEST-22-16845; **Editor assigned:** 18-Apr-2022, PreQC No. JCEST-22-16845 (PQ); **Reviewed:** 02-May -2022, QC No. JCEST-22-16845; **Revised:** 09-May-2022, Manuscript No. JCEST-22-16845 (R); **Published:** 16-May-2022, DOI: 10.35248/2157-7013.22.S10.353.

Citation: Seo CH (2022) Strategies for the Hair Follicle Regeneration: Extracellular Vesicles as a Novel Therapeutic Biomolecule. J Cell Sci Therapy. S10:353.

Copyright: © 2022 Seo CH. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

active effect of macrophages on HF stem cell dynamics, Rajendran, et al. showed that EVs derived from macrophages (MAC-EVs) upregulated hair-inductive molecules in DP cells and facilitated hair growth, which has ever not been reported [16]. The canonical Wnt signalling activation results in the nuclear translocation of β-catenin and the transcription of downstream hair-inductive gene. A recent study showed that perifollicular macrophages activate DP cells through canonical Wnt ligands and prolong the anagen phase of human HF [17]. From the previous MAC-EVs study, we have put our focus on EVs, expecting them as novel secretory molecules for the crosstalk between macrophage and DP cells. We analysed the Wnt3a, Wnt7b expression of MAC-EVs compared to that of macrophage itself. Interestingly, Wnt3a and Wnt7b were even far enriched in MAC-EVs than macrophage, and more than 95% them were associated with the membrane of MAC-EVs. The Wnt3a and Wnt7b stimulated the receptors on DP cells (such as Frizzled and LRP5/6), which readily activated Wnt/β-catenin signalling pathway. This was also verified by the mRNA expression analysis of downstream target genes (Axin2, Lef1). With the treatment of 20μg MAC-EVs, Axin2 was 6-folds upregulated and Lef1 was 40-folds upregulated. Moreover, the MAC-EVs significantly enhanced the proliferation, migration, and levels of hair-inductive markers (such as alkaline phosphatase and versican) of DP cells. Additionally, MAC-EVs increased the levels of the survival protein Bcl-2 as well as phosphorylated AKT. DP cells treated with MAC-EVs elevated the expression of VEGF and keratinocyte growth factor (KGF), which is stimulatory paracrine factors for the proliferation of surrounding matrix cells and so, prompt hair shaft growth.

CONCLUSION

Studies on extracellular vesicles as novel therapeutic tools have been rapidly growing. Our findings underscore the feasibility of EVs which are easily isolated from macrophage immune cells and furthermore suggest a possibility of EVs as a topical medication. To reserve the clinical avenue of EVs, it is necessary to elucidate the effective components in them and scrutinize the novel biological mechanisms in a comprehensive manner together with Wnt/β-catenin signalling.

ACKNOWLEDGEMENT

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science & ICT(2017M3A9G405295).

CONFLICT OF INTEREST

Author has declared that he has no conflict of interest.

REFERENCES

1. Carrasco E, Soto-Heredero G, Mittelbrunn M. The role of extracellular vesicles in cutaneous remodeling and hair follicle dynamics. Int J Mol Sci. 2019;20:2758.
2. Ohyama M, Veraitch O. Strategies to enhance epithelial-mesenchymal interactions for human hair follicle bioengineering. J Dermatol Sci. 2013;70(2):78-87.
3. Kang BM, Kwack MH, Kim MK, Kim JC, Sung YK. Sphere formation increases the ability of cultured human dermal papilla cells to induce hair follicles from mouse epidermal cells in a reconstitution assay. J Invest Dermatol. 2012;132:237-239.
4. Higgins CA, Chen JC, Cerise JE, Jahoda CAB, Christiano AM. Microenvironmental reprogramming by three-dimensional culture enables dermal papilla cells to induce de novo human hair-follicle growth. Proc Natl Acad Sci. 2013;110:19679-19688
5. Seo CH, Kwack MH, Kim MK, Kim JC, Sung YK. Activin A-induced signaling controls hair follicle neogenesis. Exp Dermatol. 2017:26(2);108-115.
6. Seo CH, Kwack MH, Kim MK, Kim JC, Sung YK. Impairment of hair-inducing capacity of three-dimensionally cultured human dermal papilla cells by the ablation of STAT5 Ann Dermatol. 2019;31(2):228-231
7. Kwack MH, Ahn JS, Jang JH, Kim JC, Sung YK, Kim MK. SFRP2 augments Wnt/β-catenin signalling in cultured dermal papilla cells Exp Dermatol. 2016;25(10):813-815
8. Kwack MH, Seo CH, Gangadaran P, Ahn BC, Kim MK, Kim JC, et al. Exosomes derived from human dermal papilla cells promote hair growth in cultured human hair follicles and augment the hair-inductive capacity of cultured dermal papilla spheres. Exp Dermatol. 2019;28(7):854-857
9. Seo CH, Kwack MH, Lee SH, Kim MK, Kim JC, Sung YK. Poor capability of 3D-cultured adipose-derived stem cells to induce hair follicles in contrast to 3D-cultured dermal papilla cells. Ann Dermatol. 2016;28(5):662-665
10. Wu J, Yang Q, Wu S, Yuan R, Zhao X, Li Y, et al. Adipose-derived stem cell exosomes promoted hair regeneration. Tissue Eng Regen Med. 2021;18:685-691.
11. Hu S, Li Z, Lutz H, Huang K, Su T, Cores J, et al. Dermal exosomes containing miR-218-5p promote hair regeneration by regulating β–catenin signaling. Sci Adv. 2020;6(30):1685
12. Riche A, Aberdam E, Marchand L, Frank E, Jahoda C, Petit I, et al. Extracellular vesicles from activated dermal fibroblasts stimulate hair follicle growth through dermal papilla-secreted norrin. Stem Cells. 2019;37(9):1166-1175.
13. Rajendran RL, Gangadaran P, Bak SS, Oh JM, Kalimuthu S, Lee HW, et al. Extracellular vesicles derived from MSCs activates dermal papilla cell in vitro and promotes hair follicle conversion from telogen to anagen in mice. Sci Rep. 2017;7:15560
14. Castellana D, Paus R, Perez-Moreno M. Macrophages contribute to the cyclic activation of adult hair follicle stem cells. PLoS Biol. 2014;12:1002002
15. Wang X, Chen H, Tian R, Zhang Y, Drutskaya MS, Wang C, et al. Macrophages induce AKT/-catenin-dependent Lgr5+ stem cell activation and hair follicle regeneration through TNF. Nat Commun. 2017;8:14091
16. Rajendran RL, Gangadaran P, Seo CH, Kwack MH, Oh JM, Lee HW, et al. Macrophage-derived extracellular vesicle promotes hair growth. Cells. 2020;9(4):856
17. Hardman JA, Muneeb F, Pople J, Bhogal R, Shahmalak A, Paus R. Human perifollicular macrophages undergo apoptosis, express Wnt ligands, and switch their polarization during catagen" J Invest Dermatol. 2019;139(12):2543-2546.