Scientific contribution/Review

The role of Extracellular Vesicles in Alopecia and its Treatment

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Abstract:
Extracellular vesicles are cell-derived membranous bodies that function as intercellular communicators, carrying proteins, lipids, DNA and RNA molecules. Many therapeutic approaches have focused on using extracellular vesicles, due to smaller risk compared to invasive cell-based therapies. Hair follicles are skin appendices that are composed of epidermal and mesenchymal component, with the former including a major reservoir of epithelial stem cells. Hair follicles continuously cycle, undergoing consecutive phases of resting, growing, and regression. Many molecules carried by extracellular vesicles are involved in the control of the hair follicle cycle and stem cell function. Thus, investigating the role of extracellular vesicles as signaling bodies potentially involved in hair cycling may be an important step in the attempt to design future alopecia treatment strategies.

Keywords: Alopecia; Hair growth; Hair regeneration; Hair follicle morphogenesis; Stem cell extracellular vesicles; Telogen to anagen transition

Citation: Tehovnik J. The role of extracellular vesicles in alopecia and its treatment. Proceedings of Socratic Lectures. 2021; 6: 94-97. https://doi.org/10.55295/PSL.2021.D.013

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1. Alopecia

Hair loss (alopecia) is a common problem in adults. Alopecia mostly affects males in their 20s, starts on the forehead and continues spreading towards the back of the scalp. Alopecia often represents a negative psychological effect on affected individuals. The most important factor in the development of alopecia is genetics, in addition, the phenomenon is also influenced by hormonal changes, vitamin deficiency and medication (the most common being chemotherapy) (Phillips et al., 2017). Alopecia can also be iatrogenic in which the reason is unknown. Modern medicine allows us to slow down alopecia, especially with drugs such as finasteride and minoxidil. Finasteride is a drug that inhibits testosterone 5-alpha reductase and is used to treat hair loss, as well as prostate hypertrophy (Phillips et al., 2017). Minoxidil is used as an antihypertensive and is used topically to treat hair loss, as it activates the beta-catenin pathway, which in turn leads to faster regeneration of hair follicles (Phillips et al., 2017). Both drugs have proven to be effective, but are only intended to improve hair loss in the short term. In addition, discontinuation of therapy can result in rapid hair loss (Phillips et al., 2017). Therapeutically, there are also various surgical procedures in which hair is aesthetically transplanted from more densely overgrown areas (Phillips et al., 2017; Khanna, 2008). It is usually an autologous transplant. The disadvantage of transplantation is the limited number of hair follicles (Khanna, 2008), and transplantation requires aggressive drug therapy (for example corticosteroids), so we are looking for new ways to treat hair loss.

Hair grows in three stages (Murphrey et al., 2021). The hair cycle begins with the anagen phase - the growth phase of the hair follicle. It is the proliferation of follicle epithelial cells in the hair follicle, which then differentiate and form hair in the follicular root cells (Murphrey et al., 2021). The next phase is the catagen phase, in which the supply of nutrients to the hair follicle from the bloodstream is interrupted (Murphrey et al., 2021). The cycle ends with the telogen phase, in which the hair follicle falls out (Murphrey et al., 2021). The dermal papilla cells located in the papilla of normal human hair follicles play a crucial role in the dermal–epidermal interactions that control hair production and events of the hair growth cycle (Murphrey et al., 2021). Dermal papilla cells manage hair follicle cycling through interacting between endothelial cells, stem cells and stem cells of the hair follicle (3). A defect in any one of the cells can lead to hair loss. Thus, restoration of these cells for better interaction is considered a potential therapeutic strategy for treating hair loss.

2. Extracellular vesicles

Extracellular vesicles are membrane nanovesicles measuring 30-1000 nanometres in diameter, which are secreted by most body cells into extracellular fluid (Doyle and Wang, 2019). They contain proteins, lipids and nucleic acids. Extracellular vesicles are composed of exosomes and microvesicles (Doyle and Wang, 2019). Exosomes are synthesized intracellularly, and form vesicle-containing endosomes. They are called multivesicular bodies. These fuse with the plasma membrane and excrete their contents into the extracellular. Cells can communicate on short and further distance via extracellular vesicles. Studies have shown that exosomes play a key role in intercellular signalling, which is important in a variety of physiological and pathological processes (Doyle and Wang, 2019).

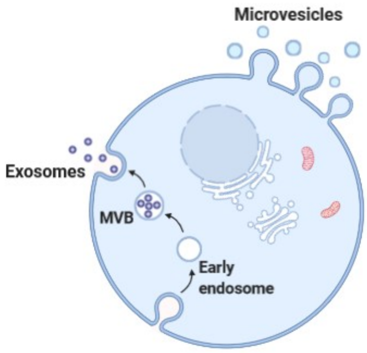

Figure 1. Extracellular vesicles - exosomes and microvesicles.

3. Potential pathways of extracellular vesicles derived treatment in hair cycle

Wingless and Int-1 (Wnt) factors are the most important regulators of hair follicle morphogenesis and hair growth. Namely, epidermal Wnt ligands play a main role in wound-induced de novo hair formation in adult skin (Carrasco et al., 2019). Consequently, they have been pointed out as potential targets for the treatment of hair-related syndromes like alopecia. Active Wnt factors have been identified as exosome-secreted molecules which can be contained in the interior compartment of these vesicles as well as transported exteriorly (Carrasco et al., 2019). Several studies have demonstrated that Wnt signaling in recipient cells can be mediated by the transition of the proteomic contents of extracellular vesicles (Carrasco et al., 2019). Additionally, Wnt signalling has been found to be activated in target cells by extracellular vesicles containing both β-catenin, the major effector protein of the Wnt pathway (Carrasco et al., 2019). For instance, Wnt4 enhances Wnt/β-catenin signaling and promotes angiogenesis. In agreement with these observations, an upregulation in the expression of Wnt3a and Wnt5a has been found in mouse skin treated with intradermically-injected extracellular vesicles obtained from mesenchymal stem cells (Carrasco et al., 2019; Rajendran et al., 2017)

MicroRNAs (miRNAs) are small noncoding RNA molecules which are capable of altering gene expression post transcriptionally and are typically transported in extracellular vesicles. These molecules have been implicated in the control of hair follicle development through the modulation of Wnt signaling, but the mechanism is not entirely understood (Carrasco et al., 2019).

An interesting area are mesenchymal stem cells in the field of cell regeneration, due to the great potential for self-renewal and the possibility of differentiation. The extracellular vesicles of mesenchymal cells have a proven anticancer effect and can also promote angiogenesis, which would be particularly useful in patients with ischemic disease (Rajendran et al., 2017). Thus, they could be used for ischemic tissue regeneration after cerebral / cardiac infarction. Many studies have shown that cytokines and dermal papilla growth factors play a role in regulating hair growth (Rajendran et al., 2017). The cells of the dermal papilla have the ability to release growth factors into the environment, which in turn signals the epithelial cells to divide, the end result of which is the growth of hair and the acceleration of hair regrowth (Rajendran et al., 2017). According to research, after treatment of these cells with extracellular vesicles of mesenchymal cells, the expression of VEGF and IGF-1 increased (Rajendran et al., 2017). VEGF has been shown to promote hair growth, increase follicle size and increase the thickness of the hair itself (Rajendran et al., 2017). IGF-1 is secreted by the cells of the dermis, as well as the cells of dermal papillae of the hair follicle, and when stimulated, hair growth is accelerated. Lastly, intradermically injected mesenchymal stem cells extracellular vesicles have been shown to favor telogen to anagen transition in a mouse model (Carrasco et al., 2019; Rajendran et al., 2017).

3. The role of macrophages' extracellular vesicles in hair growth and regeneration

A recent study identified the involvement of perifollicular macrophages in the activation of skin epithelial stem cells, as an additional signal that regulates hair follicle growth (Rajendran et al., 2020). Another study showed that macrophages induce hair follicle growth through tumour necrosis factor (TNF)-induced AKT/β-catenin signaling in Leucine-rich G-protein-coupled receptor 5 hair follicle stem cells (Rajendran et al., 2020). Human perifollicular macrophages maintain the anagen stage (making the hair follicle stronger) in humans by activating dermal papilla cells by secreting Wnt proteins (Rajendran et al., 2020). It was shown that macrophages' extracellular vesicles promote proliferation and the activation of the Wnt/β-catenin signaling pathway in dermal papilla cells (Doyle and Wang, 2019, Rajendran et al., 2020). The macrophages' extracellular vesicles enhanced the hair-inductive properties of dermal papilla cells by increasing the levels of hair-inductive proteins and survival/proliferation markers (Rajendran et al., 2020). Further experiments revealed that macrophages' extracellular vesicles promote hair growth through stimulation of vascular endothelial growth factor (VEGF) and keratinocyte growth factor (KGF) in dermal papilla cells (Rajendran et al., 2020). Macrophages' extracellular vesicles accelerate hair growth by increasing the number of hair follicle s and dermis thickness. The extracellular vesicles derived from macrophage could be excellent candidates for stimulating hair growth in humans, since their isolation from the same patients is relatively simple and less invasive than isolation of mesenchymal stem cells from the adipose tissue or bone marrow.

4. Conclusions

The emergent role of extracellular vesicles in hair follicle cycle dynamics is likely to become a high-impact tool in cosmetic medicine. For patients suffering from alopecia, extracellular vesicles isolated from autologous mesenchymal stem cells may represent a solution in the future. Nevertheless, many investigations should be done before the clinical use of extracellular vesicles, namely the most suitable cell type for isolation of extracellular vesicles (despite the fact that mesenchymal stem cells represent a very good prototype), the optimal concentration and mode of entry (intradermal or topical), the mode of treatment itself, the frequency of dosing and the duration of treatment.

Conflicts of Interest: The author declares no conflict of interest.

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