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Cellular Heterogeneity Facilitates the Functional Differences Between Hair Follicle Dermal Sheath Cells and Dermal Papilla Cells: A New Classification System for Mesenchymal Cells within the Hair Follicle Niche

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Abstract

Mesenchymal stem cells (MSCs) are known for their self-renewal and multi-lineage differentiation potential, with these cells often being evaluated in the regulation and maintenance of specific cellular niches including those of the hair follicle. Most mesenchymal stem cells in the hair follicles are housed in the dermal papilla (DP) and dermal sheath (DS), with both niches characterized by a broad variety of cellular subsets. However, while most previous studies describing the hair follicle mesenchymal niche treated all DP and DS cells as Hair Follicle Mesenchymal Stem Cells (HF-MSCs), the high number of cellular subsets would suggest that these cells are actually too heterogenous for such a broad definition. Given this we designed this study to evaluate the differentiation processes in these cells and used this data to create a new set of classifications for DP and DS cells, dividing them into "hair follicle mesenchymal stem cells (HF-MSCs)", "hair follicle mesenchymal progenitor cells (HF-MPCs)", and "hair follicle mesenchymal functional cells (HF-MFCs)". In addition, those cells that possess self-renewal and differentiation were re-named hair follicle derived mesenchymal multipotent cells (HF-MMCs). This new classification may help to further our understanding of the heterogeneity of hair follicle dermal cells and provide new insights into their evaluation.

Keywords Mesenchymal stem cells · Hair follicle · Hair follicle progenitor cells · Dermal papillae · Dermal sheath · Cellular differentiation

Introduction

Mesenchymal stem cells (MSCs) are known for their self-renewal and multi-lineage differentiation potential, with these cells retaining the ability to differentiate into a variety of mesenchymal tissues including bone, cartilage, and fat. Scientific evaluation of these cells can be traced back to 1968 when Friedenstein et al. isolated a group of cells from the bone marrow that could grow in a whirlpool, and differentiate into osteocytes [1]. Caplan further delineated these cells, naming them "mesenchymal stem cells" and at present, the most common sources of MSCs include bone marrow, adipose, and umbilical cord tissues. In recent years, MSCs from the hair follicle have continued to garner more and more attention given their connection to the primary accessory organ of the skin the hair follicle. This follicle is composed of both epithelium and dermal tissues [2] with the

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DP and DS acting as the largest MSCs reservoirs in these organs [3, 4].

While the ability to induce and differentiate cells within the dermal niche of the hair follicles has been well documented it is worth noting that this work continues. In 1967, Oliver et al. found that DP cells could regenerate ectopic hair follicles with many subsequent studies emphasizing the importance of DP cells in inducing hair follicle regeneration [5, 6]. In the case of the DS, Oliver et al. revealed the clear induction capacity of the lower 1/3 of the DS during their hair follicle transection experiments, with these findings opening a new chapter into the study of DS function [5, 7, 8]. Several subsequent studies have also shown that DS cells also possess multi-lineage differentiation capacity [9] and follow-up studies showed that the DP/DS cells shared many similarities to the MSCs isolated from more conventional source, including adherent growth, expression of specific markers, and three-lineage differentiation [10].

However, growing evidence suggests that these hair follicle 'MSCs' are highly heterogeneous, with each subset displaying distinct differences in their ability to induce hair follicle formation and differentiation. For example, the upper segment of the DS has been shown to be unable to initiate hair regeneration [11], with subsequent research reporting that each segment of the DS demonstrates different regenerative capacity [7, 8]. In addition, the ambiguity and diversity of the markers expressed by these cells suggest that they may contain many different dermal cell groups or cell subsets with high heterogeneity [4, 12].

In addition, the application of transcriptomic and single cell sequencing analysis has helped to steadily uncover the developmental fate and heterogeneity of the various cells within this niche. He et al., investigated the relationship between integrin expression and epidermal heterogeneity as well as identified multiple epidermal cell types and their expression profiles [13]. While Takahashi et al. used single-cell resolution evaluations to characterized the anatomical, transcriptional, functional, and pathological profiles of each of the distinct epidermal, hair follicle, and hair follicle associated cell sub-populations including the melanocytes, endothelial cells, and immune cells [14]. Sennett et al. isolated hair follicle progenitor and niche cells alongside several other cells from embryonic skin and used RNA sequencing to define the gene expression signatures of each of these cell subsets within these heterogeneous tissues [15]. This was then supported by data from Ge et al. which used unbiased single-cell RNA sequencing to successfully identify the major cell populations within the dorsal skin during hair follicle morphogenesis and then used this information to construct the likely epithelium/dermal cell lineage differentiation pathways. They then used this to uncover the critical molecular pathways underlying the cell fate decisions in these tissues [16]. Additional studies using Pseudotime and RNA Velocity, single-cell sequencing and Corin-CreRT2 mouse models have facilitated increasingly detailed classification of the cell subsets within the hair follicle dermal niche differentiating between DP and DS communities and aiding the identification of the key differentiation processes in each [17–20].

Unlike the hair follicle mesenchymal stem cells, which require more refined classification, hair follicle epidermal stem cells are well explored with a focus on the characteristic, heterogeneity, plasticity and clinical application [18, 21, 22]. Here, we attempted to provide a novel classification system for hair follicle mesenchymal cells based on their differentiation process. This classification system divides these cells into three categories: "Hair follicle mesenchymal stem cells (HF-MSCs)", "Hair follicle mesenchymal progenitor cells (HF-MPCs)" and "Hair follicle mesenchymal functional cells (HF-MFCs)", and provides a novel classification for those cells with some self-renewal and multi-lineage differentiation potential describing these cells as Hair follicle mesenchymal multipotent cells (HF-MMCs) (Fig. 1).

Hair Follicle Mesenchymal Stem Cells(HF-MSCs): hfDSC

In 2014, Rahmani et al. revealed that the DS contains a group of cells enriched for cell cycle genes, such as Cdk1and Top2a and capable of self-renewal. These cells were called hfDSCs following an evaluation of their fate within the DS samples as determined by *in vivo* lineage tracing [17]. These evaluations revealed that during telogen this hfDSC pool consisted of 3–6 cells encapsulating the telogen DP, while at the beginning of anagen these hfDSCs regenerated new DS and replenished SOX2 + DP cells in response to directed DP cell apoptosis. These evaluations also showed that some SOX2 + DP cells can leave the DP downregulating the expression of LEF1 and up-regulating the expression of ITGa8. These cells were then found to congregate around the DP regions during catagen where they were able to reintegrate into the hfDSC pool for entry into telogen. In 2020, Shin et al. identified seven different cellular subsets within the hair follicle mesenchymal cell pool, including the hfDSCs, 2 DS subsets, and 4 DP subsets [19]. This study also described the application of Pseudotime and RNA Velocity evaluations and Lineage Continuum analysis for uncovering the fate of the hfDSCs within the HF dermal niche.

Thus, taken together these results show that both DS and DP tissues contain a group of cells that possess the ability to proliferate and differentiate, and reveal that these cells are replenished by the resident hfDSC population [17, 19, 20]. This suggest that hfDSCs are critical to the creatin

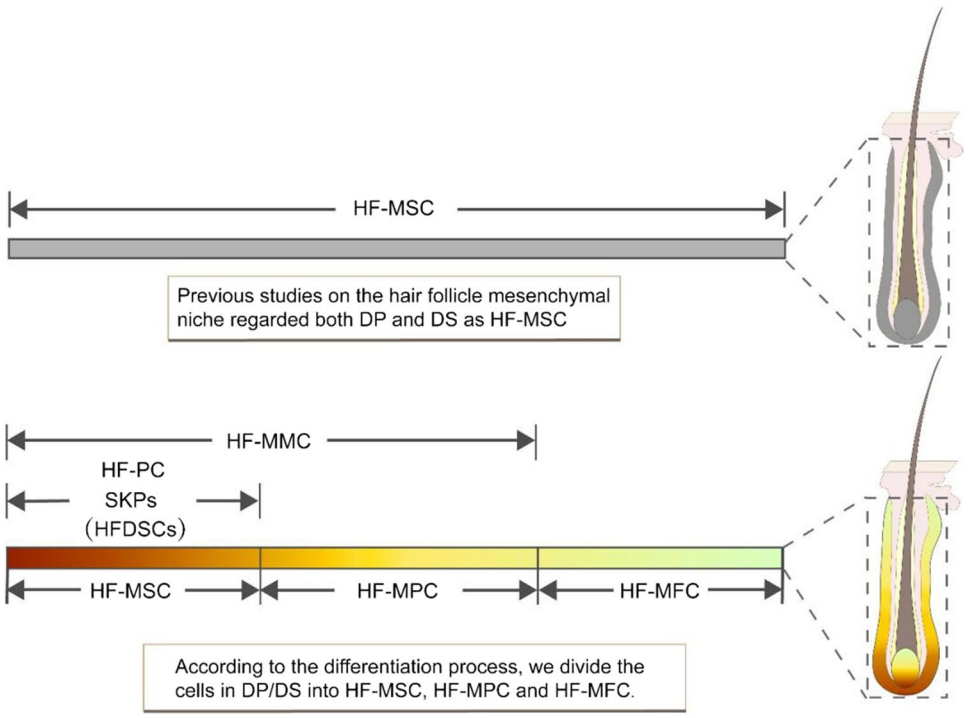

Fig. 1 Comparison of previous traditionally defined HF-MSCs and new classification of Hair follicle dermal cells. Previous studies regarded whole hair follicle dermal cells as HF-MSCs. New classification suggested HF-MSCs, HF-MPCs, HF-MFCs made up the dermal niche, re-named the traditional HF-MSCs into HF-MMC, hfDSC and SKPs are defined as HF-PCs

and regulation of the hair follicle cycle resulting in their reclassification as hair follicle mesenchymal stem cells (HF-MSCs). Thus, unsurprisingly, HF-MSCs maintain the most naive state and present with a slow cell cycle, preventing their over-consumption before maturity and reducing the potential for mutation, especially when there is no regeneration signal. This data also reveals the key role that these cells play in the maintenance and replenishment of DP and DS, both of which are critical to maintaining the stability of the mesenchymal niche. Previous studies also confirmed that hfDSCs demonstrate clear self-renewal via symmetrical cell division. Other parallel studies revealed that between the second and third anagen, about 19.8% ± 7.2% of the offspring of the HF-MSCs withdrawn from the stem cell niche underwent symmetrical differentiation to supplement DP and DS and support mesenchymal niche homeostasis [17].

Hair Follicle Mesenchymal Progenitor Cells: (HF-MPCs)

Stem cell differentiation is inevitable [23, 24] with this phenomenon being explained by one of several theories including: 1) asymmetric division: where stem cells move to a transition state and then to amplifying cell and then transit amplifying progenitor cell (TAC/ TAP); 2) asymmetric population differentiation: where progenitor cells present with a stochastic fate [25]; 3) populational asymmetry with stem cells: which is characterized by the random fate of stem and progenitor cell populations [23] (Fig. 2). (Fig. 2). While each theory has its own peculiarities all of these processes move from omnipotent to pluripotent to monopotent cell fates, with this being clearly mirrored in mesenchymal stem cell differentiation. Progenitor cells presenting in the intermediate state between stem and terminally differentiated cells are indispensable to homeostasis and often have a clearer cell fate then their less differentiated precursors.

In the case of the epidermal niche within the hair follicles, hair follicle stem cells (HFSC) produce transport magnifying cells (TACs) which are then terminally differentiated into the epidermal cell types [18]. Among these TACs some progenitor cells are assigned to their lineages immediately, while others remain in a less differentiated state, retaining their capacity for self-renewal [18]. Similarly, we believe that hair follicle mesenchymal progenitor cells (HF-MPCs) act as transitional state cells during the differentiation of HF-MSCs into DS and DP cells within the hair follicle dermis.

Most of the DP/DS cells isolated from the hair follicle mesenchymal niche presented with several of the characteristics markers for "mesenchymal stem cells" and multilineage differentiation potential. However, the quantity of HF-MSCs, 'hfDSC', was limited. This may be explained by the principle of asymmetric division [25], which suggests that the number of stem cells will not change during the process of differentiation (Fig. 3). However, Ju et al. found that true MSCs accounted for only a small portion of these cells [26] and Rahmani et al. reported that only a small number of the cells in the dermal sheath cup were actually HF-MSCs

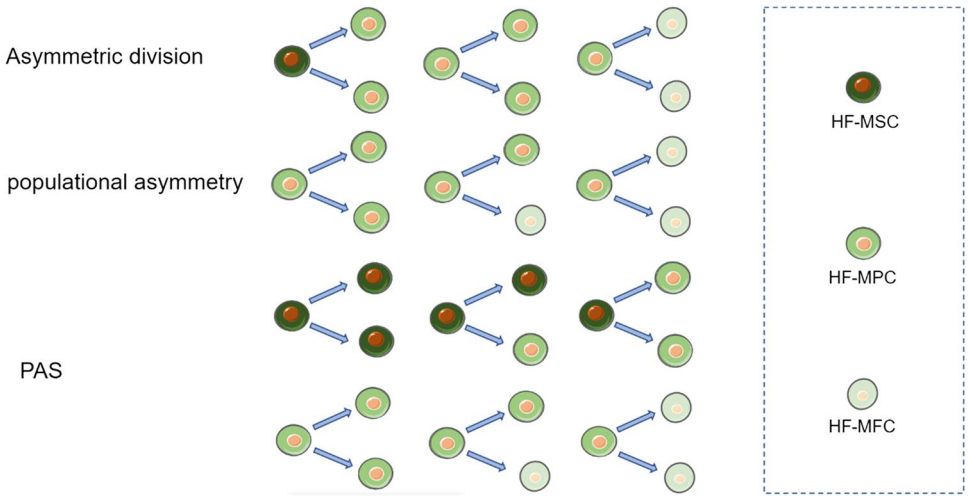

Fig. 2 Illustration of three main theories of the process of stem cell differentiation which can be referenced in hair follicle. (1) Asymmetric division: stem cells produce progenitor cells (Transport Amplification Cells, TAC) through asymmetric division. After progenitor cells proliferate, they further differentiate into terminal differentiated cells. (2) Progenitor cells have a random fate and can self renew and differentiate to produce terminal differentiated cells. (3) PAS: stem cells and progenitor cells have random fate and can self renew and further differentiate until terminal differentiation is completed

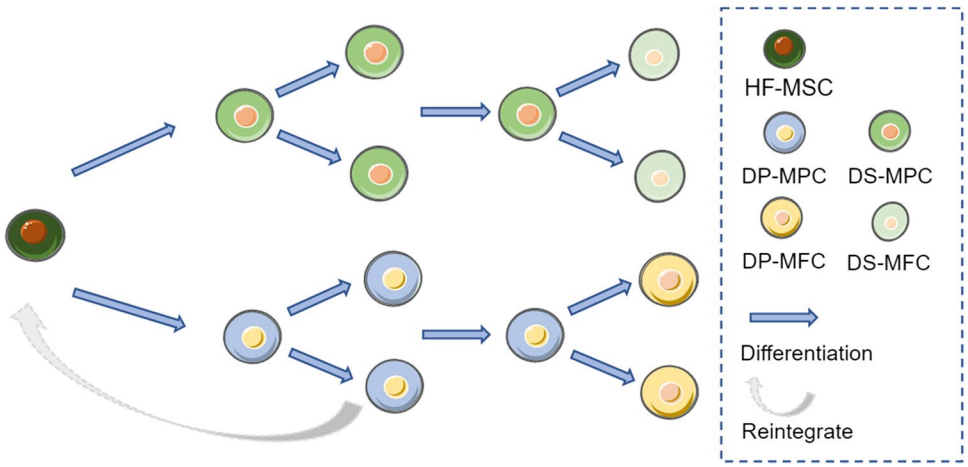

Fig. 3 Differentiation process of hair follicle mesenchymal stem cell based on Asymmetric division

and suggested that the others were precursors fated to differentiate into DP/DS cells [17]. Given this, we added a layer of classification, where cells that did not meet the criteria for classification as HF-MSCs but retained their capacity for proliferation and differentiation could be described as hair follicle mesenchymal progenitor cells (HF-MPCs). These cells fall between stem cells and terminal differentiating progenitor cells and present with relatively limited differentiation potential. When we compare stem and progenitor cells we can clearly see that progenitor cells possess a faster cell cycle, weaker capacity for self-renewal, and a higher degree of differentiation. They also demonstrated significant differences in both cell density and antigen phenotype [3, 24, 27]. HF-MPCs can further differentiate into various functional cells, enter a resting state, or induce programmed cell death during catagen [17, 19].

HF-MPCs meet the standards put forward by the Mesenchymal and Tissue Stem Cell Committee from the International Society for Cellular Therapy in 2006, including plastic adherence, expression of specific cell surface markers and ability to differentiate along the adipogenic, chondrogenic and osteogenic line-ages in vitro [28]. However, because of the complexity of the stem cell niche and the difficulties in accurately identifying and separating HF-MSCs from HF-MPCs, it's difficult to discuss the functional differences between these two cellular subsets [29]. This means that future research needs to focus on establishing the defining characteristics of these two cell types to facilitate improved separation

and evaluation of HF-MSCs and HF-MPCs function and differentiation.

Below, we further divide HF-MPCs into dermal sheath mesenchymal progenitor cells (DS-MPCs) and dermal papilla mesenchymal progenitor cells (DP-MPCs) to facilitate a clear evaluation of their distinct roles in these tissues (Fig. 4).

Dermal Sheath Mesenchymal Progenitor Cells (DS-MPCs)

DS-MPCs act as an intermediate state between HF-MSCs and DS-MFCs and are characterized by reduced self-renewal, induction and differentiation when compared to HF-MSCs. This is likely due to their further differentiation towards DS, reducing their capacity for induction and differentiation in response to changes in the physiological environment.

In addition, HF-MSCs were found to be responsible for maintaining the stemness and stability of the DS while DS-MPCs were tasked with proliferation and the reconstruction of the hair follicle dermal sheath during the growth period of each hair cycle. This set of observations were supported by a study by Aamar et al. who found that a group of progenitor cells derived from HF-MSCs presented with reduced Corin and increased α-SMA expression, making them significantly more similar to the functional cells in the DS than their stem cell counterparts [20]. These cells were located in the lower part of the hair follicle during the growth period where they facilitated rapid cell division

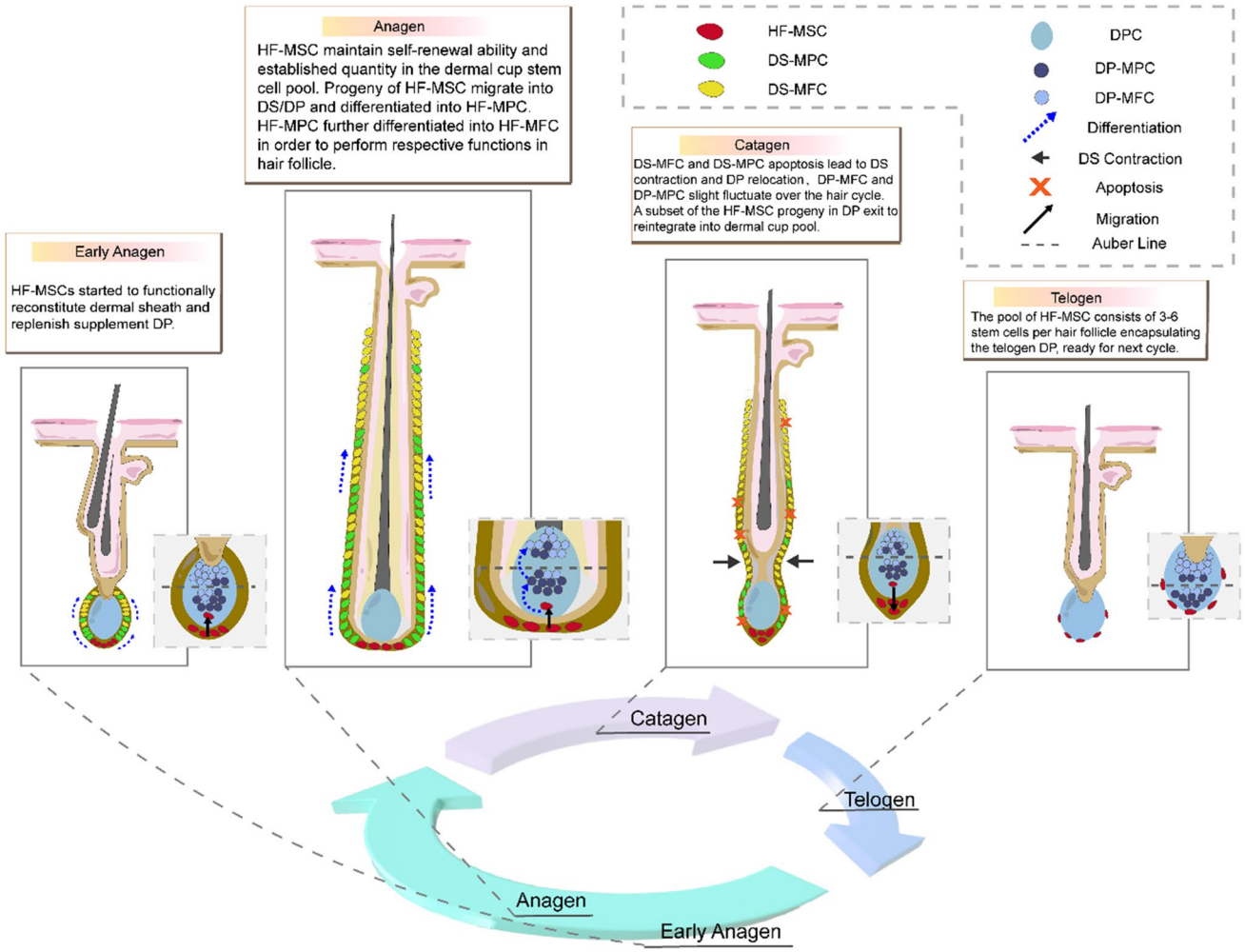

Fig. 4 Changes of newly classified hair follicle dermal cells during hair follicle cycle. At the early stage of the anagen phase, HF-MSCs which located at the stem-cell pool started to different into DS-MPCs and finally DS-MFCs to reconstitute the whole DS. Progeny of HF-MSCs migrate into DP to replenish the loss of DP-MPCs which finally differentiate into DP-MFCs. During catagen, DS-MFCs and DS-MPCs began to apoptosis, lead to DS contraction and the whole DS disappeared except HF-MSCs pool remained. DPCs keep the quantity almost constant with only slight fluctuation, a subset of HF-MSCs escaped DP and surrounded DP. During telogen, HF-MSCs re-integrate into the pool waiting for next cycle

but retained a very weak capacity for self-renewal, making them responsible for the expansion of the DS. Given this, we assigned these cells to the DS-MPCs subsets.

As noted above, the DS can be broken up into various segments with each demonstrating a different capacity for proliferation and differentiation. Thus it is not surprising that there is a difference in cell population between the lower and upper segments of the DS. The upper segment is closer to the hair follicle mesenchymal functional cells (HF-MFCs) and possesses weaker hair-regeneration capacity and differentiation potential that only can be activated under specific conditions [8].

During catagen, DS gradually undergoes apoptosis [25, 30], and DP is moved upward and relocated until it is adjacent to the hair follicle epidermal stem cells [17]. In the new growth cycle, HF-MSCs reconstitute the DS by producing various DS-MPCs subsets, facilitating continued homeostasis.

Dermal Papilla Mesenchymal Progenitor Cells (DP-MPCs)

Both DS and DP cells are very similar in their origin, induction, and differentiation with both originating from HF-MSCs [17]. However, in addition to their similar origin several studies have shown that whisker-derived DS and DP cells demonstrate significant functional overlap when evaluated using both microanatomy and transplantation experiments [5]. Similar to DS cells, the differentiation process of HF-MSCs to DP cells also moves through a specific progenitor phase, DP-MPCs. Just like DS-MPCs, DP-MPCs also demonstrate some capacity for induction and differentiation. However, because of the higher proportion of DP-MPCs, DP tissues can be more easily reprogrammed into iPS cells and used to promote hair follicle regeneration [6, 31].

This is supported by the fact that Tobin et al. found that the number of cells in the DP fluctuated despite their low rate of mitosis, suggesting some degree of proliferation [32]. However, proliferation within the adult hair follicle mesenchymal niche is largely restricted to the DS compartment with only 0.76% of DP cells per follicle shown to undergo division during early anagen [17]. Thus, the continuous depletion of primitive DP cells promotes an increased migration of HF-MSCs and their offspring into the DP during early anagen, thus supporting their capacity for replenishing DP. In addition, both Shin et al. and Tobin et al. report that some HF-MSCs migrate into the region below the Auber's line along with their offspring DP-MPCs to replenish supplementary DP [17, 32]. Then, they gradually migrate and differentiate above the Auber's line to replenish definitive DP, and finally differentiate into DP-MFCs. Among the DP-MPCs, only one subset has been shown to be able to withdraw from the DP and return to the HF-MSC niche during catagen, while all of the other cellular subsets undergo apoptosis or are maintained in the DP. When te next hair cycle starts DP-MPCs proliferate and differentiate into new DP cells in order to retain physiological function. When the number of DP cells decreases, DP-MPCs repaired the damaged DP by producing new DP cells [19].

Hair Follicle Mesenchymal Functional Cells (HF-MFCs)

Finally hair follicle mesenchymal functional cells (HF-MFCs) can be viewed as the endpoint for HF-MSCs and HF-MPCs differentiation. HF-MFCs do not have the ability to differentiate but work as the central executors of many functions within the DP and DS. These cells play a critical role in maintaining the morphology and promoting the migration of the DP niche during catagen, help to maintain the immune privilege of the hair follicles, and regulate various hair traits and signal communication with the epidermis [18, 33–36].

Dermal Sheath Mesenchymal Functional Cells (DS-MFCs)

There is a gradual transition from HF-MSCs to HF-MPCs to HF-MFCs with the DS segments of the hair follicle. DS-MFCs participate in various functions including supporting contractile function, facilitating interactions with the internal environment, and maintaining immune privilege, amongst others.

α-SMA, a common protein found in contractile cells, is highly expressed in DS cells. However, the expression of α-SMA in DS is not uniform [37], with significant heterogeneity between different cell subtypes *in vitro* [7]. In 2020, Heitman et al. used gene set enrichment analysis to show that the DS presents with similar functions and characteristics to smooth muscle and can form a stress fiber network within the hair follicle, wrapping the hair follicle with centripetal constriction force [35]. These forces may then be used during catagen to control the contraction of DS and facilitate the relocation of the DP. Subsequent evaluations using intravital 2-photon microscopy analysis found that the upper DS plays a central role in DP relocation, but not the lower DS. It is also worth mentioning that Aamar et al. compared the data of HF-MSCs with that of other cell subsets possessing low Corin and high α-SMA expression, revealing that the mesenchymal functional cells are to the process of differentiation, the higher their expression of α-SMA. Thus given the high expression of α-SMA in the upper DS and its specific contractile function, this kind

of DS cell may belong to the DS-MFCs and may play an important role in the hair follicle cycle.

There is also close communications between hair follicles and their internal environment, which is known to depend on the DS. Yoshida et al. found that vascularization genes were highly expressed in some DS cells which only exist in the upper DS. These cells likely promote the proliferation of blood vessels and endothelial cells to help regulate the formation of capillaries within the hair follicle via cell–cell contact-dependent communication. Because of its special anatomical location and function, these DS cells are also likely to fall into the DS-MFCs classification [34].

DS cells are also closely arranged within the inner longitudinal collagen layer in mouse and human hair follicles. Some scholars speculate that in addition to their secretory function these tightly arranged DS cells provide a physical barrier within the hair follicles, separating them from the various immune effectors in the skin and supporting their immune privilege [38, 39].

Dermal Papilla Mesenchymal Functional Cells (DP-MFCs)

The DP is found at the bottom of the hair follicle where it plays an important role in epithelial-mesenchymal interactions [40, 41], hair follicle regeneration, and de novo induction of hair follicle regeneration [5, 41–43]. DP-MFCs are the end point of the differentiation of DP-MPCs. However, due to the complexity of this niche, there is a clear lack of data facilitating the separation and identification of DP-MFCs and DP-MPCs.

At present, most of the studies describing the function of DP includes evaluations of both DP-MPCs and DP-MFCs. These studies include evaluations of follicle signal communication, regulation of hair stem characteristics, and immune regulation [18, 31, 41]. As for the function of each DP-MFCs subset, Rahmani et al. found that in the case of injury, cell loss, senescence, or hair type conversion, HF-MSC daughter cells were seconded to the upper DP (definitive DP), which is likely to be the basis for most of its induced functions. Several key genes related to WNT signaling (Wif1, Frzb and Bmp4), as well as Igfbp5, Ndnf and Ptch1 were significantly up-regulated in DP4 populations (definitive DP) [19]. In addition, a later study revealed that the expression of WNT signal activator, Rspo3mRNA was limited to the definitive DP. Then in 2017, Yang et al. used single cell RNA-seq to identify four different DP subsets which triggered heterogeneous epithelial-DP cross-talk between epithelial progenitor cells and DP subsets relying on different BMP and WNT signal patterns [18].

Hair Follicle-Derived Mesenchymal Multipotent Cells (HF-MMCs) Can Be Classified According to Source and Function

Given the data described above we would like to propose the following classification scheme, separating "HF-MSCs", "HF-MPCs" and "HF-MFCs" based on their differentiation. However, in addition to the HF-MSCs and HF-MPCs subsets [20], there are still many cellular subsets with no clear classification and indeterminate differentiation types. Most of these subsets exhibit some capacity for self-renewal, induction, and multi-lineage differentiation and include cells with various phenotypes such as SKPs and SOX^{2+}DP cells, amongst others. Thus, when we combined these attributes with their location awe created an additional category of cells, the Hair Follicle Derived Mesenchymal Multipotent Cells (HF-MMCs). These cells all play an important role in hair regeneration, tissue damage repair, and multidirectional differentiation *in vitro* and should be further validated *in vivo* [3, 23, 44].

Among the HF-MMCs, SKPs are the most well defined, and possess the potential to differentiate into both nerves and mesodermal tissues [45], with some more recent studies suggesting that SKPs and HF-MSCs present with similar gene expression, transcriptome, biomarker, and *in vivo* distribution and functional profiles. However, there is no evidence that these two cell types are even the same kind of cells, with a clear differentiation between the two clearly supported by the differences in their pluripotency and differentiation capacity. Given this we suggest that SKPs and HF-MSCs may be bundled together under the broader classification of Hair Follicle Derived Pluripotent Cells (HF-PCs).

SOX^{2+}/SOX^{2-}DP Cells

SOX2 is an important gene involved in the maintenance of embryonic stem cell pluripotency, with several studies reporting its strong expression in the DP. Biernaskie et al. found that the expression of SOX^2 in DPCs coincided with increased self-renewal *in vitro*, and reported that these cells facilitated the repopulation of various dermal cells, rebuilding both the DP and DS when transplanted into animals [46]. The difference in the expression levels of SOX^2 among different DP cell populations is likely associated with the difference in the appearance of different hair types including Guard hairs, awl and auchene hairs, which are both produced from SOX^2 positive DP tissues, and zigzag hairs which are produced from SOX^2 negative DP tissues [16, 47–49]. Although zigzag hairs have no SOX^2 they still proceed through the same hair follicle cycle as SOX^{2+} hair types. Given this, speculate that SOX^{2-}DP cells also are likely to display specific differentiation and

induction abilities, but their mechanism of renewal and their relationship with HF-MSCs require further evaluation.

Skin-Derived Precursor Stem Cells (SKPs)

In 2001, Toma et al. isolated a series of neural stem cells with the goal of purifying a specific class of neural crest-related stem cells from murine skin [45]. These authors described any cells that could differentiate into neurons, adipocytes, glial cells, and smooth muscle cells as skin-derived precursor stem cells (SKPs) [45, 50]. In primary culture SKPs tend to aggregate into spheres and can maintain their differentiation capacity for at least 1 year after passage. When SKPs were compared with MSCs, it was found that they have similar cell cycle distribution, CD antigen expression, stem cell markers, and differentiation capacity [45, 51].

These SKPs are also found within the human skin and hair follicle dermis, and are known to undergo both proliferation and differentiation [45, 46, 52–55]. SKPs have been broadly applied in tissue and organ repair, and are of great significance in the effective management of Hirschsprung's disease [56]. SKPs have also been shown to alleviate muscle diseases, promote diabetic wound healing, and support bone repair [57–59].

Hair Follicle-Derived Pluripotent Cells (HF-PCs)

Current research suggests that the dermal niche within the hair follicle is one of the most important sites for SKPs accumulation. Toma et al. analyzed the epidermis, dermis and nerve endings and found that SKPs originate from the dermal tissue [45]. SKPs isolated from the skin express DP-specific markers (nestin, versican, Wnt5a, etc.) [52] and DP tissues are known to include a cellular population with the same embryonic transcription factors (slug, snail, twist, etc.), proliferation status, and multi-lineage differentiation capability as SKPs. Hunt et al. proved that the hair follicle DP was rich in SKPs [55] while Biernaskie et al. found that SKPs transplanted into the back skin of mice returned to the host DP and DS, expressed the relevant markers, and differentiated into several dermal cell types such as fibroblasts and adipocytes [46].

Biernaskie et al. [46] then went on to evaluate the characteristics of both SKPs and HF-MSCs derived from the hair follicles and found that these two cells were extremely similar in terms of their transcriptomic and functional characteristics. Gene chip analysis showed that the correlation between HF-MSCs and SKPs samples was as high as 0.86–0.94 (in-sample analysis showed that the correlation between HF-MSCs and SKPs samples was 0.91–0.99 and 0.96–0.99, respectively). However, it is still not known whether SKPs and HF-MSCs are the same type of cells or if they simply share a high degree or functional overlap. Other questions include whether there is a sequence in the differentiation process.

Based on these results we suggest that these cells retain their independent classifications but suggest that they may fall into a broad category of cells which should be defined as Hair Follicle-Derived Pluripotent Cells (HF-PCs) based on their source, ability, and high similarity. Both of these cellular subsets demonstrate self-renewal and maintain strong pluripotency making them critical participants in the hair cycle and regeneration processes.

Stem Cell Markers in the Hair Follicle

Until recently there was some debate as to whether hfDSCs could be found within the human HF. However, recent studies suggest that while there are significant structural differences between human and mouse hair follicles, the process of cell differentiation should be the same in these models. Given this, some scholars speculated that human follicles contain a multilayered DS, possibly supporting the existence of an expanded hfDSC pool in these systems [60]. However, most of the markers and genes for these cells need to be evaluated at a single cell level with most of these findings focused on murine models, thus the specific localization and expression of various stem cell markers require further evaluation in human samples. That said, we believe that more attention should be paid to the specific markers, functions, and types of cells, including the HF-MSCs, HF-MPCs or HF-MFCs found in the follicle. To this end Table 1 lists the major clusters of differentiation in skin-derived stem cells from the hair follicle, with the majority of these cells coming directly from the dermis. These cell include hfDSC, SKPs, MSCs, DS, DP, and a variety of epidermal-derived stem cells, including epidermal Hair follicle stem cells (HFSCs).

Future Prospects and Clinical Significance

MSCs were first identified as potential therapeutic agents by Hillard Lazarus in 1995 [69], following their demonstration of the feasibility and effectiveness of MSCs transplantation in humans. Since then, the clinical application of cell therapy has developed rapidly, with the focus of these studies

Table 1 markers of stem cells in hair follicle [4, 10, 17, 19, 34, 46, 61–65]

	Markers		Species	Reference
	+	-		
hfDSC	ITGa8 and CD200		Mouse	[10, 66]
SKPs	Nestin, Fibronectin, Vimentin, Slug, Snail, Twist, Pax3, Sox9, sox2		Mouse and human	[17]
DPC	ITGa8 (supplementary DP) CD133 CD90, AP, Corin, LEF-1, ITGa9, noggin, versican	ITGa8 (definitive DP)	Mouse Mouse Human	[4, 19, 67]
DSC	α-SMA (increasing in upper DS) ACAN, ITGa8, Stmn2, Tnmd, Mgp(lower DS), EDNRB, CD36(upper DS) CD 29, CD 44, CD90, CD133 CD10		Mouse Mouse Human Human	[17, 31, 61, 68]
MSC	CD44, CD73, CD90, α-internexin, NG2, CD29, CD105 CD105, CD73, CD90	CD34 CD45, CD34, CD14 or CD11b, CD79a or CD19 or HLA-DR	Mouse Human	[43]
HFSCs	keratin15 CD34, Krt19, Lgr5, transcriptional factors Gli1, Sox9, Hopx, Nfatc1, Tcf3 and Lhx2 CD200 and CD59 CK 15, CD29, and CD49f	CD24, CD34, CD71 and CD47 CD34 and CD117	Mouse and human Mouse Human Human	[62, 68]

expanding to include multi-lineage differentiation [70, 71], trophic activity [72], vascularization [73], and immunomodulation [74]. Thus when we combine these effects with the low ethical cost of using MSCs, it is clear to see why they are under broad evaluation for application in hair disease. DP cells [75], dermal sheath cups [44] and Micrografts Enriched with Autologous Human Follicle Mesenchymal Stem Cells [76] could significantly increase the hair density.

However, there are still several barriers to the active promotion and application of MSCs in clinical intervention including the lack of marketing approval in the United States [66]. The most important issues hampering MSCs therapies include their heterogeneity, and the lack of a reproducible, predictable, standardized therapeutic approach to MSCs amplification for clinical treatment.

MSCs derived from different tissues demonstrate a high degree of heterogeneity [67], with many studies describing differences in the therapeutic effect of MSCs isolated from different tissues or using different protocols. These differences are largely explained by the high degree of heterogeneity in MSCs. A prime example of this is the two Human Umbilical Cord Mesenchymal Stem Cell (hUC-MSC) subpopulations, referred to as hUC-MSC1 and hUC-MSC2, isolated by Wang. These two populations displayed clear differences in colony forming potential, adipogenic and osteogenic differentiation, with one population more effectively protecting the retinal structure and facilitating the rescue of the visual function of the affected animal [26] than the other, highlighting the heterogeneity of MSC culture. A subsequent study, evaluating two subsets of rat bone marrow mesenchymal stem cells (rBMSC), rBMSC1 and rBMSC2, isolated by Li [68]. revealed that one isolation, rBMSC1, demonstrated increased proliferation, stronger colony formation, and better adipogenic potential then the other isolation, which translated to differences in their treatment outcomes for retinal degeneration in a rat model. Similarly, in hair diseases, cell grafts including all three subsets "HF-MSCs", " HF-MPCs" and "HF-MFCs" demonstrated significantly different therapeutic effects than individual subgroups.

This means that the further study of MSCs heterogeneity is critical to its effective clinical application (Table 2). For example, if we can classify the subsets of hair follicle mesenchymal stem cells using our nomenclature system, "HF-MSCs"-" HF-MPCs" -"HF-MFCs", and explore their extraction methods, characteristics and functions we might be able to select cell subsets with unique characteristics specifically designed to meet the needs of different kinds of hair diseases and achieve effective cell therapy. This heterogeneity may well be a significant positive for MSCs as it may allow for the very specific application of cellular subsets to reduce potential unwanted effects improving precision and clinical utility. This in turn would significantly improve the safety, reproducibility, and predictability of these cell therapies, and lay a solid foundation for standardized treatment. While the concept of precise cell therapy has significant implications for hair disease, it also might facilitate an expansion in the broader field of cell based therapy.

Table 2 Pros and cons of the current and last classification

	Advantage	Disadvantage
Last classification	1. Containing a large number of cell subsets with a certain ability of differentiation and regeneration 2. The classification method is simple 3. Definite cell markers	Composed of heterogeneous cell sebsets
New classification	1. More accurate classification 2. To provide reference for further research of the differentiation of stem cells in hair follicles 3. It is solid foundation for standardized treatment and precise cell therapy	1. The cell markers of each subsets need to be explored 2. Various cell subsets in each classification (HF-MSC, HF-MPC, HF-MFC) need to be further explored

Conclusion

Based on the current research, we propose a novel classification system for hair follicle MSCs including "HF-MSCs", "HF-MPCs" and "HF-MFCs" with delineation determined by the degree of differentiation (Fig. 3). Traditional "HF-MSCs" contain several cell types and should be re-defined as HF-MMCs which includes both HF-MSCs and HF-MPCs subtypes. In addition, the pluripotency and derivation of SKPs and HF-MSCs suggest that these two sub types likely belong to a larger family we would like to refer to as Hair Follicle Derived Pluripotent Cells (HF-PCs). It is our hope that this new classification may help further the study of hair follicle mesenchymal cells and facilitate more precise cell therapy in the future.

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Declarations

Conflicts of Interest The authors declare that they have no conflicts of interest.

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