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Involvement of hair follicles in skin tumorigenesis, skin homeostasis and wound healing

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ABSTRACT

Hair follicles play a crucial role in skin tumorigenesis, skin homeostasis, and wound healing. They contribute in several ways whereas in the bulge region epidermal stem cells give rise to both normal and malignant skin cells. If mutated, they can potentially lead to skin cancer as is seen in basal cell carcinoma and squamous cell carcinoma, common forms of skin cancer. Various growth factors, such as Wnt, Hedgehog, and Notch signalling pathways, regulate hair follicle development and cycling and dysregulation of these pathways can lead to abnormal cell proliferation and differentiation, contributing to cancer development in hair follicle cells. The stem cells within hair follicles contribute to the regeneration of both the epidermis (outer skin layer) and the hair follicle itself. The regenerative capacity of hair follicles can speed up wound healing by providing a pool of cells that can be recruited to the injured area to promote tissue repair. Hair follicles also modulate the inflammatory response during wound healing by secreting cytokines and growth factors, that orchestrate the healing process by regulating inflammation, angiogenesis, and collagen deposition, but in chronic wounds their role can be disrupted. When the hair follicles are damaged or not activated properly during the healing process, abnormal scarring or fibrosis can occur, leading to the formation of thick, fibrous scars rather than functional skin. The aim of this review is to provide an overview of the many roles played by the hair follicle and its associated structures as well as its close association with the skin.

Introduction

Hair follicles play a crucial role in skin tumorigenesis, skin homeostasis, and wound healing. The hair follicle (HF) is an important mini organ supporting many biological functions such as protection against cold and potential injuries, thermal insulation, camouflage, sebaceous dispersion, sensory perception, social interactions, immune response against pathogens, angiogenesis, neurogenesis, wound healing, affecting the quality of life, attractiveness and self-esteem. The HF is a unique miniature organ in mammalian skin that undergoes continuous regeneration cycles comprising the anagen, catagen, and telogen phases.[1,2] Hair follicles are central to skin homeostasis as they undergo cyclical processes that influences the turnover of skin cells, is tightly regulated and maintains skin structure and function by replacing old skin cells with new ones. Hair follicles are essential in the wound healing process, particularly in the regeneration of the skin after injury where they play a pivotal role in wound healing via a process of skin reprogramming, where the follicle stem cells temporarily take on the role of regenerating the skin tissue.

Biology of the hair follicle

Structurally it is a tube-like structure that extends from the epidermis (outer layer of skin) into the dermis (deeper layer of skin) and consists of several layers, including the outer root sheath, inner root sheath, and the hair shaft itself. It is composed of two main components, the upper part comprises the infundibulum and the isthmus, and the lower part comprises the bulb, matrix, and dermal papilla (DP). The hair bulb is located at the base of the follicle and contains actively dividing cells that produce new hair. The dermal papilla is a cluster of specialized fibroblasts at the base of the follicle that regulate hair growth while the sebaceous gland waterproofs the skin by secreting sebum to lubricate the hair and skin and is attached to the follicle. Attached to the hair follicle is the arrector pili muscle which it causes hair to stand up when contracted. The hair bulge is housed in the isthmus and is said to be where stem cells are located causing regeneration of the HF under homeostatic conditions or following injury. These cells migrate from the bulge toward the bulb, where they proliferate and differentiate to produce the hair shaft and all the epithelial cells that constitute the HFs.[3] Other cells that make up the hair follicle include keratinocytes which produce keratin and melanocytes which produce melanin, giving hair its colour. There are several concentric layers, from outermost to innermost. Surrounding the entire follicle is the connective tissue sheath which provides structural support, while the outer root sheath (ORS) that is continuous with the epidermis, forms the outermost layer of the follicle proper. The inner root sheath (IRS) consists of three layers, Henle's, Huxley's and an innermost layer interlocking with the hair follicle. The visible part is the hair shaft which is made up of a cuticle, cortex and the medulla. The lowermost part is the hair bulb containing the matrix and dermal papilla.

The hair follicle undergoes numerous cycles of growth and retraction throughout life and is made up of three distinct phases: anagen, catagen, and telogen, each regulated by different signals. The active growth phase is the anagen lasting 2-7 years for scalp hair. On the scalp, anagen may last as long as 8 years resulting in long hair, but in other places, such as the eyebrow, anagen may be as short as 3 months. The second phase is the catagen or the regression phase lasting about 2 weeks where the majority of the HF cells undergo apoptosis causing shortening of the lower compartment and bringing the DP cells closer to the bulge. Cells that escape apoptosis comprise the reservoir that leads to the next anagen. Telogen is also known as the resting phase, lasting about 3 months, after which the hair falls out. It is estimated that at any given time 5%–15% of HFs in the scalp remain in telogen. [1,2,3] Growth is regulated by hormones such as androgens, estrogens, and thyroid hormones, various signalling molecules that control follicle development and cycling, blood supply providing nutrients and oxygen, and sensory nerve endings making hair sensitive to touch and movement. Complex interactions between various signalling pathways, transcription factors, and epigenetic regulators, all work together to control the hair growth cycle.[4]

Location of Hair Follicle Stem Cells

Hair follicle stem cells (HFSCs) are located in the bulge just below the sebaceous gland as well as in the hair germ, located between the bulge and the dermal papilla. These cells are multipotent, slow cycling normally to be maintained over time, remain quiescent until they are coaxed to proliferate and/or differentiate only when needed and cycle independently after birth. Under homeostatic conditions, these cells are maintained through asymmetric division, where the parent stem cell divides into two cells with varying differentiation potential: one retaining the stem cell characteristics (self-renewal), and the other assuming a more differentiated phenotype (differentiation). They are identified by the presence of specific markers CD34, Lgr5, and K15.[5,6,7] During anagen they migrate in the bulb region where they are induced to proliferate and differentiate to all epithelial cell types of the HF.[8,9] The single bulge cells are highly clonogenic and are capable of generating intact follicles in vivo,[10,11] thus providing evidence that the bulge harbours true stem cells and not a collection of progenitors. Cells that are LGR5 + seem to be the first to respond to the inductive signals in early anagen and start proliferating and differentiating. Greco et al. found that hair germ cells proliferate faster than bulge cells and are the first to respond to DP signals at the late telogen. [12] However, they lose their proliferative capacity faster than bulge cells during long-term expansion in vitro. The same study demonstrated that some cells committed to differentiate, return to the bulge and appeared to regulate the activity of bulge stem cells by secreting key factors.[2] In addition to hair regeneration, bulge stem cells were found to contribute to wound healing following skin injury by migrating and differentiating into epidermal keratinocytes.[13,14] The HFs also harbours melanocytes, which differentiate and produce melanin during each hair cycle stimulating hair pigmentation. These were identified by Nishimura et al. in the bulge and sub-bulge areas and were slow-cycling, undifferentiated cells that were activated during anagen to produce melanocytes.[15] Cells isolated cells from the area between the bulge and the sebaceous gland (isthmus/infundibulum) were found to be distinct from the bulge-derived stem cells, did not express bulge-specific markers, such as KRT15 and CD34 but

maintained high clonogenic potential in vitro, actively proliferating in vivo, could generate new follicles, suggesting that quiescence might not be a requirement for maintaining multipotency.

Stem cells residing in the bulge region migrate and also give rise to resident gland cells. This theory is supported by transplantation studies showing that bulge cells generated functional sebaceous glands in vivo. Another study suggests that stem cells located above the bulge differentiate into sebocytes.[16,17,18] These 2 theories were combined by Horsley et al. who identified a population of cells in the region of the sebaceous gland expressing a transcription factor BLIMP1 with the potential to differentiate into sebocytes. When BLIMP1 is absent, HFs resulted in the activation of bulge cells and this is further supported by implantation of bulge stem cells led to BLIMP1 + cells in the bulge.[18] Within the DP and dermal sheath are cell populations that regulate hair cycling by exchanging signals with the bulge.[19] A recent study showed that DP/DS stem cells are the precursors of dermal stem cells and contribute to dermal maintenance and wound healing.[19,20,21]

Hair follicle stem cells (HFSCs) are crucial for initiating each new hair cycle and at the start of anagen become activated, proliferate and downward to form the new hair follicle and hair shaft. They are activated by signals from the dermal papilla and the surrounding environment with the key signalling pathways involved in activation including Wnt/β-catenin, BMP, and Sonic Hedgehog. The balance between activating and inhibitory signals determines when stem cells will initiate a new hair cycle.[20] They give rise to all epithelial components of the hair follicle, produce cells for the outer root sheath, inner root sheath, and the hair shaft itself and also contribute to the sebaceous gland and the epidermis during wound healing. Dysfunction of HFSCs lead to various hair disorders, such as hair loss. Thus, these cells are promising targets for hair restoration therapies. Researchers are exploring ways to activate dormant stem cells or transplant cultured stem cells to treat hair loss.

Skin stem cells

The skin is the largest organ of the body covering an average surface area of 1.85 m2 and accounting for ~15% of total body weight and has an array of functions, acting as a barrier for protection and prevention of dehydration, as a sensory and thermoregulatory organ, and as an active site of vitamin D synthesis and immune surveillance.[22] The skin is composed of two main layers, i.e., the epidermis and the dermis and accessories, such as hair, nails, and sweat, and sebaceous glands.[23] The skin is also populated by nerve receptors for responses to external stimuli like touch, heat, pain, and pressure. [24] The different layers have different thicknesses depending on their anatomical location. It may be very thin in the eyelids (0.1 mm) or thicker in the palms and soles of the feet (1.5 mm). The dermis can be ~30–40 times thicker in the dorsal area than the corresponding epidermal layer.[25] Further division is noted in the epidermis which houses the keratinocytes, dendritic cells, melanocytes, Merkel's cells, and Langerhans' cells, known as stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum respectively. It is in the inner-most part of the epidermis[25,26] that different populations of stem cells (SCs) are located, from which through extensive proliferation and differentiation, the skin and its auxiliary structures are generated such as nails and sweat glands.[27] The basal cell layer is not the only stem cell niche within the skin. Niches are also found within the hair follicle (HF), interfollicular epidermis (IFE), and sebaceous glands.[27] The hair follicle is a downward protrusion from the epidermis. These stem cells also contribute to wound repair, restoration of tissue integrity and function of damaged tissue. Homeostasis is meticulously regulated by all of these diverse niches. The HFSCs play a pivotal role in sustaining skin homeostasis through interactions with the vasculature, nerves, and the extracellular matrix (ECM). The stem cells within the skin are usually named after the niche in which they reside in, i.e., hair follicle stem cells (HFSCs), melanocyte stem cells (MeSCs), interfollicular epidermis stem cells (IFESCs), and dermal stem cells (DSCs). Regardless of their niche, these cells are collectively known as skin stem cells (SSCs).

The main task of these SSCs is to replace, restore, and regenerate the epidermal cells either lost, damaged, or pathologically dysfunctional.[28,29] This requires a carefully orchestrated cell division, to both maintain the stem cell pool and produce lineage-committed cell precursors.[30] Skin stem cells (SSCs) were thought to be age-resistant, mostly because their number does not seem to dwindle through time[31,32] but we now know that they do eventually become unstable or dysfunctional and display a lower differentiation and self-renewal capacity.[33] As mentioned, SSCs are found in diverse niches within the skin, of which the hair follicle bulge has been the most studied. In addition, SSCs can also populate the sebaceous glands, which is thought to be unipotent and dedicated to the renewal of the sebocytes' pool.[34,35] The other niches in the compartments of the dermal papilla (DP) and the dermal sheath (DS)[43,36] display a greater differentiation capacity into cells of ectodermal, mesenchymal, and endodermal lineages[37,38,] even being able to differentiate into cells of hematopoietic lineages.[36]

Signalling Pathways

There are several signalling pathways associated with the development and regeneration of the skin. The most relevant one is the Wnt, which regulates cell proliferation, differentiation, migration, and polarity.[39,40] Somewhat unique Wnt signalling drives skin development and maintenance through both canonical and non-canonical signalling cascades.[41, 42] Nineteen (19) Wnt genes have been identified in the human genome[42] secreting proteins into the extracellular environment and binding to the frizzled (Fz) family of receptors (e.g., lipoprotein receptor-related proteins 5 and 6 [LRP-5/6], receptor tyrosine kinase like orphan receptor 2 [ROR2], and receptor like tyrosine kinase [RYK]) to activate various signalling pathways.[43,44] Proteins such as Dickkopf protein (Dkk), secreted frizzled-related protein (SFRP), or Wnt inhibitory factor (WIF) block Wnt receptors and regulate the activation of the signalling cascade.[45,46] Wnt signalling can also be modulated by R-spondin and leucine-rich repeat-containing G-protein coupled receptor proteins.[47,48] The early skin tissue displays a

dynamic crosstalk between the epidermis and the dermis during embryonic development that drives the formation of the basement membrane, the stratification of the epidermis, and the formation of the HF.[49]

Wnt proteins engage Frizzled (Fz) receptors on the cellular membrane, instigating downstream signalling events. Upon binding of the Wnt ligand to its receptor, inhibition of the destruction complex occurs, preventing β-catenin phosphorylation and degradation which then results in the accumulation of β-catenin in the cytoplasm which is then translocated to the nucleus where it associates with T cell factor/lymphocyte enhancer, thereby activating target genes. This initiates the anagen phase and a repertoire of genes intricately linked to the process of HF growth is initiated.[50,51] The activation of TGF-β/BMP signalling pathway triggers a spectrum of cellular responses, encompassing cell proliferation, differentiation, apoptosis, as well as the synthesis of the ECM.[52,53] These are two closely related classes of cytokines functioning as signalling molecules that mediate cellular communication, by binding to their respective receptors, resulting in their phosphorylation and formation of an activated Smad protein complex and in the nucleus engages with other transcription factors to intricately regulate the transcription of specific genes. Notably, the BMP antagonist, Noggin, emerges as an instrumental factor in the regulation of HFSCs as it intricately interacts with Noggin to finely modulate the differentiation of HFSCs, guiding them towards the development of sebaceous glands, sweat glands, and epidermal cells through the overexpression of lymphoid enhancer-binding factor (LEF) molecules.[54] Another cellular mechanism is the Notch signalling pathway which serves as a regulatory mechanism governing cell proliferation, differentiation, and fate decisions.[55,56] This signalling pathway promotes the differentiation of HFSCs into HF cells while concurrently inhibiting their differentiation into epidermal cells through the Notch/RBP-J mechanism.[57,58] Additionally the Notch signalling pathway functions as a downstream pathway of Wnt/β-catenin signalling, activating the transcription of target genes such as hair and split enhancers (Hes), runt-associated transcription factors (Runx), and Notch inhibitory membrane proteins (Numb).[59] Yet another conserved mechanism of cellular signalling, the Hedgehog signalling pathway, is imperative for the activation of β-catenin activity.[60] All these signalling pathways intricately interact, forming a finely tuned regulatory network to govern the activities of HFSCs.

As a crucial ecological niche within the skin, HFSCs possess the capacity to interact with other niches, contributing to the maintenance of skin homeostasis and regulate hair growth. The normal functioning of HFSCs necessitates an adequate vascular supply for essential elements such as oxygen, nutrients, and various growth factors[61] with the lymphatic system removing tissue waste and supporting immune surveillance for HFSCs[62] thereby ensuring functionality of HFSCs and involves cell signalling, niche maintenance, and participation in the healing process. Therefore, ensuring an adequate blood supply may prove crucial for the maintenance of HF health and the prevention of hair loss. Nerves and neurons are also activated by sympathetic nerves[59,63,64,65] constitutes a complex network, encompassing various aspects such as neuroendocrine regulation, neurovascular regulation, and neural-immune interactions. The ECM, comprising components such as collagen, integrins, proteoglycans, and other structural macromolecules, serves as a tissue scaffold that offers crucial structural support and play a pivotal role in cell adhesion, migration, and cell signaling.[66] The ECM encompasses a diverse array of proteins, polysaccharides, and other biomolecules that collectively construct a microenvironment essential for the survival and optimal functioning of HFSCs.[67,68,69,70,71,72] Overall the interaction between HFSCs and other skin niches forms an integrated regulatory network.

Wound healing

The skin is an essential component in the protection against environmental hazards such as UV light, pathogenic agents, and dehydration and this continuous exposure can compromise its integrity. The health and maintenance of the skin is tightly regulated through the secretion of diverse cytokines, chemokines, growth factors, and the activation of specific signalling pathways.[73,74] Skin maintenance therefore depends upon the proliferation and differentiation of the basal layer of the epidermis, which gives raise to suprabasal cells, the granular layer, and finally to the stratum corneum. Skin wound healing is a highly organized and coordinated process that results in the restoration of tissue integrity and functions. Any interruption in the normal wound-healing process can lead to the development of non-healing chronic wounds. Many factors can cause a delay in wound healing such as venous or arterial insufficiency, diabetes, renal disease, trauma, advanced age, tissue hypoxia, ischemia, foreign bodies, maceration of tissue, exudates, infection, including compromised nutritional or immune status and local pressure effects, that disrupt the regulation of the inflammatory process.[75] The increased prevalence of non-communicable diseases such as diabetes, obesity, and vascular disease are also contributing factors that give rise to chronic wounds. These have resulted in a major global issue with significant management costs. In the United States alone, more than 6 million people afflicted with chronic wounds, place a major burden on the health care system, with an estimated annual cost of $25 billion.[76,77] Fifteen percent of diabetic patients suffer from diabetic foot ulcers (DFUs), leading to to lower-leg amputations.[75,78] Accumulating experimental evidence suggests that the use of stem cells as a potential wound therapy is gaining widespread recognition.

Therefore, wound healing and skin regeneration are indispensable for the health and survival of higher organisms. After injury, re-epithelialization should occur as soon as possible to prevent the loss of the barrier function. Wound healing processes include inflammation, blood clotting, cellular proliferation, and extracellular matrix (ECM) remodelling.[79,80] During the inflammatory phase, the wound is sealed by fibrin, forming a temporary matrix occupied by immune cells whose task is to remove dead tissue and control infection. This followed by recruitment of fibroblasts that secrete collagen, form granulation tissue, and promote angiogenesis and the recruitment of fibroblast-derived myofibroblasts, which contract the wound area. The basal cell subpopulations

express keratin 14 and involucrin into the wound area, the former of which have greater proliferation and differentiation potential and, thus, survive for longer periods in comparison with the latter.[81] In addition specific progenitor cells within the bulge, upper bulge, sebaceous gland junction, and infundibulum of the hair follicle are able to differentiate into epidermal cells and, thus, contribute towards skin regeneration.[82] Keratin15 expressing SSCs within the bulge/secondary hair germ

migrate toward the centre of a wound after full epidermal excision[83,84] and once there adopt an epidermal phenotype, disappearing thereafter, suggesting involvement during the acute phase of injury. Finally, new ECM components are secreted by both fibroblasts and epidermal keratinocytes, to remodel the matrix through the expression of matrix metalloproteinases (MMPs). In this way, the regenerated skin tissue is able to regain ~80% of its normal strength in as little as 3 to 4 months. In mammals, wound healing results in the formation of scar tissue without any of the original appendages (i.e., hair follicles, nails, and glands) but however the basic functions of the skin regarding protection against pathogens and dehydration. Extensive scarring can sometimes occur affecting the quality of life of the afflicted individual. Extensive research is ongoing to find ways to fully restore the skin to its original state.

Skin stem cells and cancer

The type of skin cancer a person gets is determined by where the cancer begins. The most common type of skin cancer is Basal cell carcinoma which begins in basal cells. This type of cancer develops in people who have fair skin who have been exposed for years to the sun or from indoor tanning. BCCs appear like a flesh-colored round growth, pearl-like bump, or a pinkish patch of skin and are common on the head, neck, and arms and these can form anywhere on the body, including the chest, abdomen, and legs. Squamous cell carcinoma (SCC) of the skin is the second most common type of skin cancer, often appearing as red firm bumps, scaly patch, or a sore that heals and then re-opens. Skin stem cells (SCCs) tend to form on skin that gets frequent sun exposure, such as the rim of the ear, face, neck, arms, chest, and back. SCC can also arise from actinic keratoses.[85,86] The third type, Melanoma, is the most serious because it has a tendency to spread and develops within a mole that present on the skin or appears suddenly as a dark spot on the skin that looks different from the rest. Other types include Merkel cell skin cancer, a rare form of skin cancer caused by an overgrowth of Merkel cells and is as dangerous as Melanoma as it can spread. Other types include cutaneous lymphoma (white cell that grows irregularly) and Kaposi's sarcoma.

Skin cancer occurs when mutations develop in the DNA of your skin cells. These mutations cause skin cells to grow uncontrollably and form a mass of cancer cells. It is most common in people over 30 years old but has also been seen in children and young adults.[87] Different epidermal and dermal populations contribute to cancer in different ways. Oncogenic β-catenin signalling is one illustration depending on the epidermal SC type that stabilises the expression of β-catenin, and different tumours are formed. Others include Lgr5$^+$ population, which promotes formation of pilomatricomas (benign HF skin tumours), while Lrig1$^+$ cells develop trichoadenomas (a rare benign follicular tumour with cornifying cysts) and the Lgr6$^+$ population gives rise to dermatofibromas within the IFE.[88] It has also been shown that with activation of Hedgehog signalling only basal Krt14$^+$ cells in the IFE and HF infundibulum can initiate basal BCC formation[89,90] and BCC initiation and progression are highly dependent on expression of the transcription factor Sox9.[91] However we take note that for squamous cell carcinoma (SCC), more than one epidermal population can induce SCC.[92] Skin stem cells also have distinct open chromatin landscapes from distinct SC lineages[93] implying an lineage infidelity that can persist during malignant progression, promoting uncontrolled growth and heterogeneous tumour cell behaviour.[93,94]

Mutant epidermal cells can engage nontransformed (healthy) cells via Wnt ligand secretion to induce aberrant growth of the whole tissue.[95] But there is a tumour protective mechanism innately whereby healthy epithelial cells recognize, surround, and eliminate mutant cells to restore tissue homeostasis, to prevent over proliferation and tumour initiation.[96] The molecular mechanisms however are still unclear.

The tumour microenvironment contains both tumour-promoting and -inhibitory effects as well as endothelial and immune cells and cancer-associated fibroblasts (CAFs). These CAFs play an important role in the evolution of solid tumours and originate from different mesenchymal populations (which can be normal fibroblasts, MSCs and transdifferentiated epithelial and endothelial cells). Cancer-associated fibroblasts (CAFs) reside within the tumour and can also infiltrate the tumour mass. They can proliferate, migrate and secrete growth factors and ECM modulators and get deposited on the ECM.[97.98] These cells are heterogeneous and show enrichment of similar gene ontology classes such as cell adhesion, immune response and ECM modulation, suggesting that different cell types under similar conditions perform similar tasks and are maintained by a combination of genetic mutations, epigenetic alterations, and persistent environmental effects. In mice they have shown that the main contributor of CAFs are the CD26$^+$ fibroblasts in a skin melanoma xenograft model.[99] To date the not much is known about how these different fibroblast lineages contribute to tumour stroma formation.

Cancer Stem cells (CSCs) are tumour cells that exhibit stem cell-like properties and are primarily defined by the ability to initiate tumours. Cancer Stem cells (CSCs) may not be multipotent, leading to single lineage tumours, such as SCC (epidermal lineage), various follicular tumour types (hair follicle lineage), or sebaceous gland tumours (sebaceous lineage). Slow-cycling bulge SCs can acquire genetic mutations, such as Kras mutations or Smad4 deletions, and this drives them into hyperproliferation.[100] Depending on the tumour type and experimental models used to assess tumour initiation, their numbers vary from ≤1% to approximately 20%.[101,102,100] In an SCC mouse model, it was noted that CSCs were rare but can increase dramatically in metastatic SCCs and SCCs with epithelial

to mesenchymal transition.[100] Surface markers are used to sort these cells as but not limited to include CD34[103], CD200[104], CD49f[105], CD44[106] and CD133.[107] Aldehyde dehydrogenase (ALDH) and ABC transporter activity can also be used to sort CSCs. Apart from these, side population (SP) assay is used to identify stem-like cells based on their ability to pump out Hoechst dye and chemotherapeutic drugs via ABC transporters.[108,109]

Genetic mutations also have distinct effects on CSC behavior with the main target being K15. Kras G12D in keratin 15 initiates benign papillomas, and when combined with a heterozygous Ptch deletion, BCC is induced, and if p53 is lost, the situation is exacerbated.[110] In combination with Smad4 deletion tumours of other lineages, such as basal cell carcinomas, trichoepitheliomas, and sebaceous adenomas[100] can also be induced. As not all genetic mutations driven by the same K15 promoter cause multilineage tumour types, specific stem cell mutations also play an important role in determining tumour lineages. Epigenetic regulation, such as DNA methylation, histone acetylation, and miRNA expression, also plays an important role in skin SC and CSC behaviors. Enhancer of zeste homolog 2 is required for epidermal CSC survival, migration, invasion, and tumour formation.[111,112] miRNAs maintain SC populations and many are downregulated (miR-203)[113] or silenced.[114] Some are overexpressed (mi-R9) resulting in the expansion of metastasis-associated CSCs.[100]

The microenvironment also controls CSC fate. Normally quiescence limits proliferation and protects genomic integrity,[115,116] but in this state, CSCs may contribute to cancer progression by increasing epithelial to mesenchymal transition, enhancing colony formation, invasion, and tumour initiation.[117] Quiescent CSCs are delayed in entering late S phase. They have high DNA repair activity and are more resistant to therapeutics or promote DNA damage-induced cell death.[118,119,120]

What we get from the above is that SC and CSCs do share some features, but they are less location dependent and genetic alterations make them more aggressive. Abnormalities in genetic and or epigenetic mechanisms can lead to the development of cancer, and their plasticity is associated with transcription accessibility for genes that are normally expressed in different tissues.

Melanoma is the third most common type of skin cancer that is heterogeneous, composed of genetically divergent subpopulations existing as cancer stem-like cells (CSCs) and many non-cancer stem cells (non-CSCs). These cells have unique characteristics and surface proteins with aberrant signalling pathways that are responsible for melanoma progression, drug resistance, and recurrence. Melanomas harbour significant alterations in functional genes (BRAF, CDKN2A, NRAS, TP53, and NF1). A master regulator of melanocyte homeostasis is a microphthalmia-associated transcription factor (MITF) and this factor is not only associated with the development of melanoma but is also essential for the regulation of genes for survival,[121] cell cycle control,[122] invasion,[123] autophagy,[124] senescence bypass,[125] and DNA damage repair and chromosome stability.[125,126] To survive in the human body, melanoma cells undergo genetic, epigenetic, and/or phenotypic modification. Melanoma has the highest mutation frequency among human cancers, thus causing extensive heterogeneity because of genomic instability and aberrant signalling pathways linked to the development of genetically divergent subpopulations[127,128] with the most common being subpopulations bearing mutant (Mut) protein and its wild-type (WT) counterpart. Similarly, too epigenetic intertumoral heterogeneity.[129] This ability to switch between CSC and non-CSC states is the plasticity that allows for long-term tumour growth.[130] There are many biomarkers of CSCs, such as CD271, that is characterized by its ability to metastasize to the brain.[131] Overexpression of CD271 induces quiescence[132,133,134,135,] and hence, loss of CD271 expression leads to phenotype switching in melanoma.[134] Normal B cell surface markers are elevated, while transcription factors, Nanog and Oct3/4 are markedly elevated in melanospheres when compared to adherent melanoma cells[136,137] as is Sox10 expression. Normal signalling pathways such as Wnt, and Notch and Hedgehog are also activated in melanoma CSCs.[138,139,140,141] Many have also shown that increased CD133 expression is associated with high tumorigenicity and metastatic potential for melanoma cells[142,143,144,145] and is also involved in the regulation of tumour resistance. This marker is associated with poor prognosis in various cancers[146] due to its exhibited resistance to chemotherapy and radiation therapy. It has been suggested that CD133 is a key tumour progression and treatment-resistance-driving signalling protein in melanoma,[147] this occurs via the binding of PI3K, p85, to the Tyrosine 828 (Tyr828) residue located on the cytoplasmic domain of the CD133 protein.[147] Cancer Stem Cells (CSCs) also possess immune evasion strategies mediated by CSC-secreted immunosuppressive factors, thus allowing CSCs to evade anti-tumour immune-mediated reactions.[148] Cellular senescence is another autonomous tumour suppressor mechanism that allows tumour cells to evade the toxicity of anti-cancer agents and subsequently grow and metastasize.

Conclusion

The presence of multiple pools of long-term SCs and progenitors that reside in the skin epithelium has made us realise that cells are capable of exhibiting plasticity and changing their fate through dedifferentiation, as well as changes in cell-intrinsic properties and responses to different microenvironments. This intracellular heterogeneity together with the availability of single-cell gene expression profiles to researchers s become available together with tools to make these datasets readily accessible, there will be a greater appreciation of the significance of cellular heterogeneity. Computational modelling of experimental data allows for rigorous evaluation of data quality and also allows for newer hypothesis generation. The newer concepts of micro niches and cell memory warrant further investigation, which may unravel the distinction between cell types and states. However, questions have arisen as to whether there are many more skin SCs or progenitors and if ageing influences the number or function of these different skin SCs. This may have benefits in the understanding of the behaviour and dynamics of skin tissue during development, homeostasis and disease. In

terms of CSC, the importance of the local environment, niche, in cellular plasticity as well as mechanisms that influence wound repair and cancer progression are highlighted particularly the role of CSCs in melanoma progression, drug resistance, and recurrence. This heterogeneity, CD20, is less location dependant and genetic alterations may lead to more aggressive cancers. However therapeutically, interventions can be designed to target specific functions of CSC populations responsible for metastasis. Melanoma progression and treatment resistance is mostly associated with the development of genetically divergent subpopulations that can be identified via specific markers. Being central to tumour development, drug resistance, and recurrence, these genetic and epigenetic changes lead to the deregulation of signal transduction pathways, thus exerting pressure which may have been induced by treatment targeted through pathway-inhibition, thus resulting in triggering activation of the other signalling cascades.

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