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Graying of the human hair follicle

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Synopsis

Quality of life in our society depends crucially on healthy aging, a hallmark of which is the graying hair follicle. During anagen melanocyte precursors migrate to the hair bulb to form the pigmentary unit where they mature and synthesize melanin. Melanin is transferred to the hair shaft forming keratinocytes giving the hair its colour. Graying is the process in which distinct mechanisms lead to deterioration of the hair follicle melanocyte population. We briefly review the hair graying process and state that the aging hair follicle is a valid model for tissue specific aging and a promising target to test therapeutic intervention.

INTRODUCTION TO HAIR GRAYING

Social acceptance in our society depends crucially on visible perception of a person's health status. It is therefore most people's intention to manipulate the visual signs of aging as soon as they arise. This is the reason why we dye our hair when it becomes gray (canities). The market turn over rate of hair colorants is estimated at around 12–13 billion Euros per annum. Chemical hair colorants are easy to use and effectively covering gray hair. However, their drawbacks are short lasting, damaging to hair and not able to restore the natural color of hair. Because hair graying is tightly linked with aging we hypothesize that if we understand graying, we would also understand aging and vice versa. For these reasons it has been a focus of academic and corporate research to understand the biological mechanisms of hair graying, and the ability to slow down the graying process or restore the natural pigmentation of hair. Nevertheless there are hardly any treatment concepts available to date that act satisfyingly against hair graying.

Establishment of the pigmentary-unit and hair follicle pigmentation is tightly linked to the hair follicle's growth cycle (1,2). Recruitment of melanoblasts occurs during early anagen. At the top of anagen, in full growth phase, the pigmentary-unit is formed: melanocytes mature atop the dermal papilla tightly anchored to the basement membrane separating the epithelial from the mesenchymal compartment of the hair follicle, pigment

is produced and in close collaboration with hair follicle keratinocytes it is transferred to the hair shaft. During late anagen, the pigmentary-unit starts to disassemble leading to resolution of the pigmentary unit during catagen (Figure 1), a process which repeats itself many times during a life-time and is characterized by the gradual reduction of melanocytes active in the pigmentary-unit. In humans we distinguish between premature and senile canities. Senile canitites is believed to occur because of exhaustion of the regenerative capacity of hair pigmentation as well as through programmed events during aging. Premature canities can be viewed as caused by environmental factors, inflammation or psycho-emotional stress.

In terms of hair-graying it is well established that oxidative stress is a trigger of melanocyte apoptosis in the hair follicle bulb, however not in the outer root sheath (3). It is noteworthy that oxidative stress in the hair follicle causes apoptosis selectively in melanocytes (3). Bcl-2, an anti-oxidative stress protein is required for maintenance of hair follicle melanocytes at the tip of the hair bulb (3) and lack of Bcl-2 leads to disappearance of

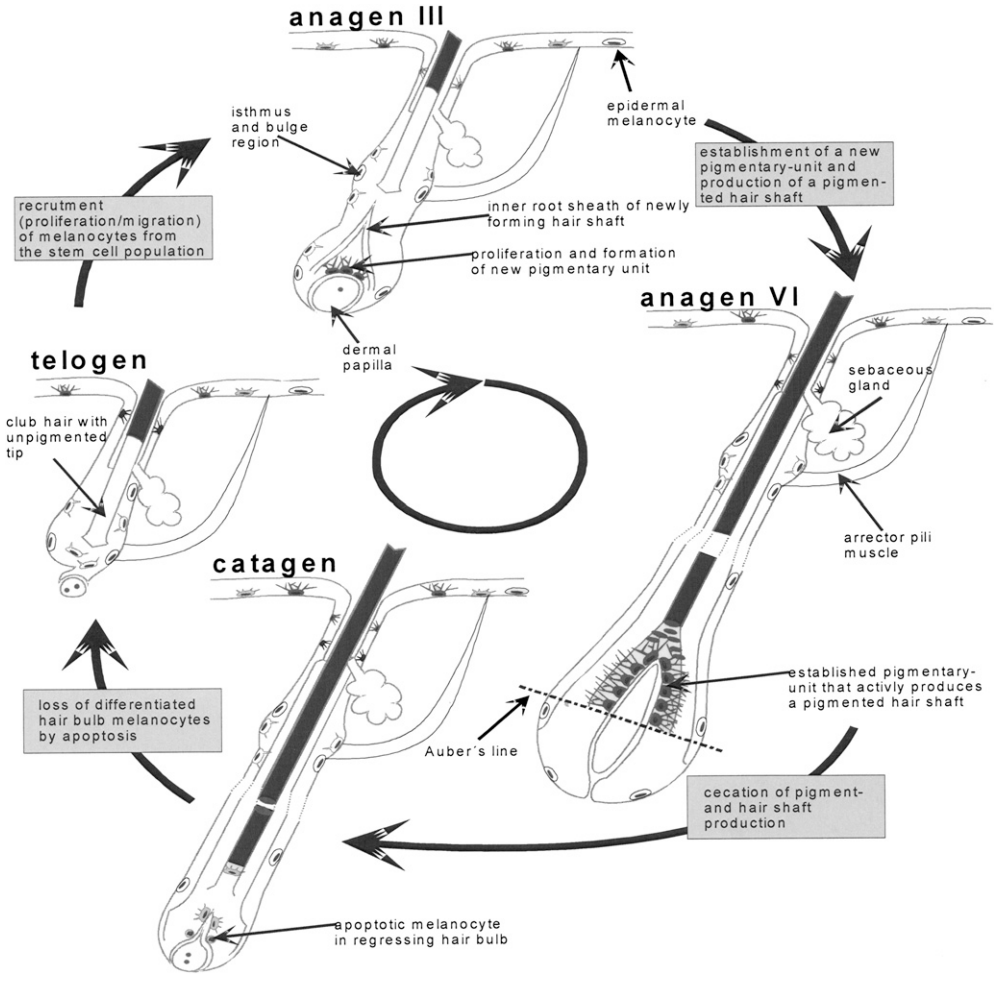

Figure 1. Scheme of the establishment and cessation of the pigmentary unit during the hair growth cycle.

melanocyte precursors in the stem cell niche in mice (4). In addition, gray hair follicles have almost absent catalase and methionine sulfoxide reductase expression (5) and are hence not able to fight oxidative stress dependent deterioration of hair follicle melanocytes.

Establishment of a pigmentary unit requires various biological mechanisms. Melanocyte precursors (melanoblasts) must be recruited from the bulge which is the stem cell niche in the hair follicle (4,6). From there they must migrate down the outer root sheath (ORS) to the hair bulb and home at the tip of the dermal papilla above the Auber's line where they form the pigmentary unit. Melanoblasts must differentiate into mature melanocytes, synthesize melanin, the pigment that gives the hair its color, and pack the melanin into melanosomes. The melanosomes travel out to the tips of the melanocyte's dendrites where they are transferred to keratinocytes.

This complex mechanism is steered by gene expression and factors regulating hair follicle melanocyte biology. Silencing of the receptor for stem cell factor c-kit was shown to block establishment of a pigmentary unit in hair follicles (7,8). This shows nicely that hair follicle melanocytes are dependent on the growth factors and cytokines comprising the hair follicle growth milieu secreted by the epidermis and dermis surrounding the hair follicle. This growth milieu is changed constantly by intrinsic and extrinsic stimuli, and we know that during aging this milieu changes from a growth milieu into an aging milieu (9).

Since melanocytes are cells derived from the neural crest, neurotrophic factors like nerve growth factor or neurotrophin 3 can regulate melanocytes development (10). In addition, Substance P, a neuropeptide stress mediator, has been shown to be present in nerve fibers in close vicinity to stressed hair follicles, leading to apoptosis and disappearance of melanocytes from the pigmentary unit (11).

In vitro we can study and assess the pigmentation status of individual hair follicles, isolated from scalp biopsies, by light microscopy and the so called likert-Scale. With the Likert-Scale we can distinguish five grades of pigmentation from fully pigmented to white. These are assessed by defining the pigmentation status of the hair follicle's pigmentary unit (Figure 2). In fully pigmented hairs the pigmentary unit is a clear-cut pear-shaped black structure at the tip of the dermal papilla above the Auber's line. During graying melanocytes are lost, the shape of the pigmentary unit gets fuzzy, melanocytes are dislocated and appear below the Auber's line, it is possible to see the dendritic shape of the melanocytes and the dermal papilla becomes more and more visible. In white hair follicles finally there are no melanocytes left in the hair blub indicating the exhaustion of the melanocyte cell pool.

Methods to study the graying process and results that can be obtained through their application.

Two questions arise: why is there exhaustion of the regenerative capacity of hair follicle melanocytes, and how does the surrounding growth factor milieu change with age? To answer these questions and to better understand graying one would have to further characterize the molecular factors defining aging of melanocytes in the hair follicle. We speculate that within the hair follicle gene expression is altered in white and gray hair follicles compared to pigmented hair follicies. Investigation of differential gene expression should provide a base to understand the genetic determination of hair follicle aging (12). In addition, one could *in vitro* analyze the aging milieu in the hair follicle, e.g. through secreted factors (cytokines, neuropeptides, growth factors) in the growth medium or through *in loco* immunohistochemistry of pigmented versus gray or white hair follicles. One would

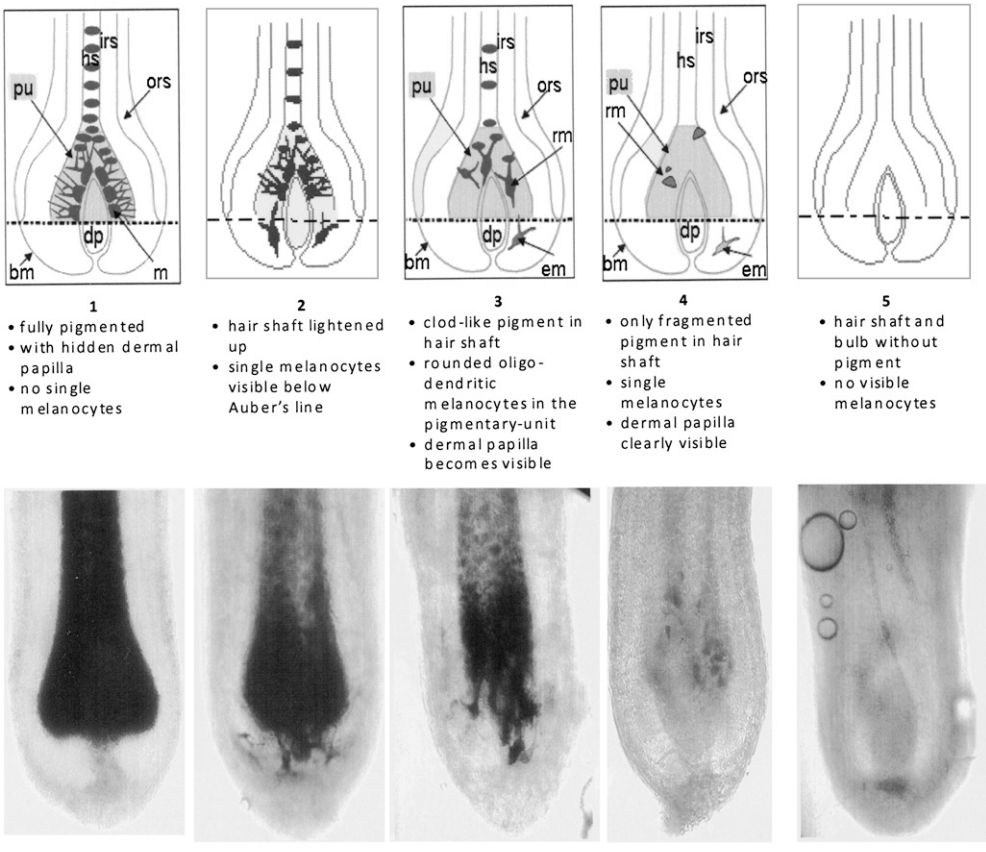

Figure 2. Differentiation of pigmentation status in the hair follicle. Five grades of pigmentation are distinguished and assessed by characterizing melanocyte density and localization in the hair follicle bulb. bm – basal membrane; dp – dermal papilla; em – ectopic melanocyte; hs – hair shaft; irs – inner root sheath; m – melanocyte; ors – outer root sheath; pu – pigmentary unit; rm – rounded melanocyte.

then be able to identify molecular targets with which to manipulate the hair follicle aging process and therefore slow down hair graying or restore gray hair to its natural colour.

We are confident that with such approaches one can specifically target genes and proteins involved in hair follicle melanocyte biology. Further investigation will elucidate novel mechanisms of hair graying and reveal promising targets for cosmetic or clinical intervention therein.

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