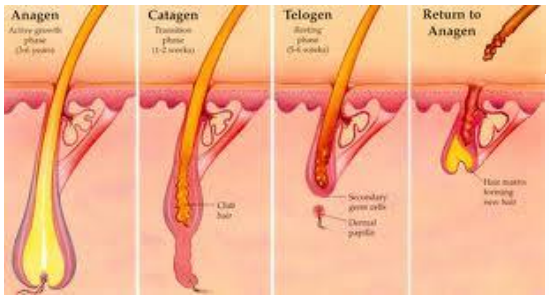
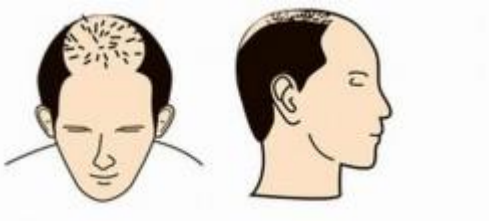
VivaCell Services

Hair growth and prevention of hair loss

VivaCell Biotechnology GmbH

Effects of natural products (extracts/compounds) on hair growth and prevention of hair loss





Investigators: VivaCell Biotechnology GmbH/Espana SL

Author and contact address:

Dr. Bernd L. Fiebich

VivaCell Biotechnology

Ferdinand-Porsche-Str. 5

79211 Denzlingen

Tel: + 49 761-4760502

Mobile: +49 179 211 5187

e-Mail: fiebich@vivacell.de

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INTRODUCTION

Hair growth is controlled by a unique repetitive cycle comprised of anagen, catagen and telogen phases. Each strand of hair on the human body is at its own stage of development. Once the cycle is complete, it restarts and a new strand of hair begins to form. The rate or speed of hair growth is about 1.25 centimeters or 0.5 inches per month, or about 15 centimeters or 6 inches per year.

Anagen phase

The anagen phase is known as the growth phase. It begins in the papilla and can last from two to six years. The span at which the hair remains in this stage of growth is determined by genetics. The longer the hair stays in the anagen phase, the faster and longer it will grow. During this phase, the cells in the papilla divide to produce new hair fibbers, and the follicle buries itself into the dermal layer of the skin to nourish the strand. About 85% of the hairs on one's head are in the anagen phase at any given time.

Catagen phase

Signals sent out by the body determine when the anagen phase ends and the catagen phase begin. The catagen phase, also known as the transitional phase, allows the follicle to, in a sense, renew itself. During this time, which lasts about two weeks, the hair follicle shrinks due to disintegration and the papilla detaches and "rests," cutting the hair strand off from its nourishing blood supply. Ultimately, the follicle is 1/6 its original length, causing the hair shaft to be pushed upward. While hair is not growing during this phase, the length of the terminal fibbers increases when the follicle pushes them upward.

Telogen phase

During the telogen, or resting, phase the hair and follicle remain dormant anywhere from 1–4 months. Ten to fifteen percent of the hairs on one's head are in this phase of growth in any given time. The anagen phase begins again once the telogen phase is complete. The preceding hair strand is pushed up and out by the new, growing strand. The process causes the normal hair loss known as shedding.

Dermal papilla cells

Dermal papilla cells (DPCs), a Group of specialized fibroblasts within the hair follicle bulb, have an essential function in the control of hair growth not only in the normal hair cycle but also in the pathogenesis of certain conditions, for example in androgenetic alopecia (AGA). Therefore, factors affecting the functions of DPCs in hair loss are of great importance from the therapeutic viewpoint

The dermal papilla is a highly active group of cells. It is derived from the dermis mesenchymal cells, located at the base of the hair follicle. The dermal papilla is implicated in controlling the hair growth cycle, be capable of inducing follicle development from the epidermis and production of hair fiber. Early passage dermal papilla cells can induce hair growth in vivo, but, upon further culturing, this property is lost. Hair growth is tightly regulated by the epithelial-mesenchymal interaction of hair follicle cells, for example, interferon beta secreted from dermal papilla cells inhibits the growth of outer root sheath cells in cultured. The survival of dermal papilla cell is also regulated by signal transduction pathways, activating both ERK and Akt promote dermal papilla cell survival.

AGA occurs in half of Caucasian men more than 40 years of age. In men with AGA, a horseshoe-shaped area of the temporal/occipital scalp region is consistently spared, thus, implying a differential end-organ response between hair follicles (HF) in balding versus non-balding scalp. Studies in the quail-chick model have shown that the dermis of the frontoparietal scalp is derived from the neural crest, whereas that of the occipital/temporal scalp is derived from mesoderm. The dermal component of the HF such as the papilla may, therefore, be of primary importance for site-specific responses to the causative factors in human AGA

Growth factors and other factors important for hair growth

Numerous DPCs-derived growth factors and cytokines have been implicated in the regulation of hair growth, including acid fibroblast growth factor, basic fibroblast growth factor, keratinocyte growth factor, hematocyte growth factor (also known as scatter factor), stem cell factor (also known as steel factor), insulin-like growth factor (IGF)-1, IGF binding protein, vascular epithelial growth factor, platelet derived growth factor PDGF, transforming growth factor- β1 and 2, IL-1β, and IL-6.

5-alpha reductase and hair loss

5alpha-reductase (3-oxo-5a-steroid-D4-dehydrogenase; 5aR), a NADPH-dependent membrane protein, irreversibly catalyses the reduction of 4-en-3-oxosteroids, resulting in the corresponding 5alpha -3-oxosteroids. The most important reaction is the conversion of testosterone (T) to the most potentandrogen 5alpha -dihydrotestosterone (DHT), which displays the highest affinity towards the androgen receptor. The irreversible reduction of T to DHT represents the final step in androgen biosynthesis. In humans, two 5a reductase isoenyzmes are expressed: 5alpha reductase type I and 5 alpha reductase type II. The isoenzymes have a different distribution pattern, which is still under discussion. In principle, type I is predominantly expressed in skin, scalp and follicles, whereas type II is mainly found in prostate tissue. However, more recent reports describe that 5alpha reductase I is the predominant form in oil and sweat glands. In stroma and basal cells of the prostate, 5alpha reductase type II is expressed, but it was demonstrated that in epithelial cells of the prostate, also 5alpha reductase I is expressed. 5a-reductase type I and type II display distinct biochemical and pharmacological properties, such as pH-optimum, Km etc. Elevated DHT levels correlate with the pathogenesis and progression of androgen-dependent diseases such as prostate cancer (PCa) and benign prostatic hyperplasia (BPH), which is the most common benign tumor affecting over 50% of men above the age of 70. Additionally, male pattern hair loss (MPHL, androgenic alopecia) is caused by an overproduction of 5alpha reductase and DHT in the hair follicles. The hair loss associated with increased levels of DHT in hair follicles is due to the effect of DHT on the cycle by which scalp hair grows; in the presence of increased levels of DHT in hair follicles, the natural hair cycle is interrupted and newly produced hairs are miniaturized rather than achieving full growth. Thus, the 5alpha reductase isoenzymes are associated with two conditions common to men: BPH and MPHL. Both conditions have been successfully treated with drugs that lower the level of DHT available to prostate tissue and hair follicles, so-called 5alpha reductase inhibitors, blocking the action of the enzyme 5alpha reductase that converts T into DHT.

Telomeres

Telomeres, the nucleotide repeats that caps the ends of eukaryotic chromosomes, serve critical roles in promoting cell viability and in maintaining chromosomal stability. Critical telomere shortening and loss of the protective telomere capping function in cell culture initiates senescence (aging). Expression of telomerase, the reverse transcriptase that synthesizes telomere repeats, is sufficient to lengthen and stabilize telomeres, thus enabling cells to proliferate in an unlimited fashion. Telomerase is expressed in stem cells and progenitor cells in self-renewing tissues,

TERT and TERC

Telomerase is comprised of two subunits: TERT, the telomerase reverse transcriptase, and TERC, the telomerase RNA component. In stem cell and progenitor cell compartments, TERT serves a critical role in maintaining telomere length and function to support tissue homeostasis. Induction of TERT in mouse skin causes a rapid transition in hair follicle from the resting phase (telogen) to the active phase (anagen) of the hair follicle cycle and robust hair growth.

Wnt/β-Catenin

The Wnt/β-catenin pathway plays an important role in the initiation, development, and growth of hair follicles. Furthermore, the transient activation of β-catenin results in hair re-growth in mice. Ablation of β-catenin results in dramatic hair shortening and abnormal regeneration of hair in the dermal papilla of mouse hair follicles. The expression of β-catenin in the dermal papilla is high in the anagen phase but low in both the catagen and the telogen phases. An interaction between β-catenin, androgen receptors and keratinocyte growth inhibition through modification of Wnt signaling by androgens has been reported to be involved in androgenic alopecia. Therefore, to identify materials that promote hair follicle morphogenesis by natural product extracts the pTOPFlash assay system, which can measure β-catenin transcription, is a common assay to screen products that promote hair growth.

Apoptosis and inflammation in hair loss

Hair loss is the consequence of hair cell apoptosis, or programmed cell death. Apoptosis is the final result of what is termed the caspase activation cascade. Essentially DHT, superoxide, and other free radicals damage the cell's mitochondria, and the damaged mitochondria in turn vomits cytochrome C, which activates the caspase cascade. TGF-beta and alpha activate caspases around hair follicles. The activated caspase cascade propagates downstream into caspase 3. Activation of caspase 3 is thought to be a direct cause of cell apoptosis (programmed cell death) in general. Protein Kinase C (PKC) as an executor of apoptosis and PKC isozymes are involved in the final execution of hair cell apoptosis in relation to caspase 3.

Sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of AGA. One of the key inflammatory mediators is tumor necrosis factor alpha (TNF-alpha)which has been demonstrated to be an inducer of PKC and thus inducing hair cell apoptosis. This pathway is known to be a major cause of hair loss. TNF-alpha is a quick acting proinflammatory cytokine, and TNF-alpha is over secreted in cases of rapid hair loss.

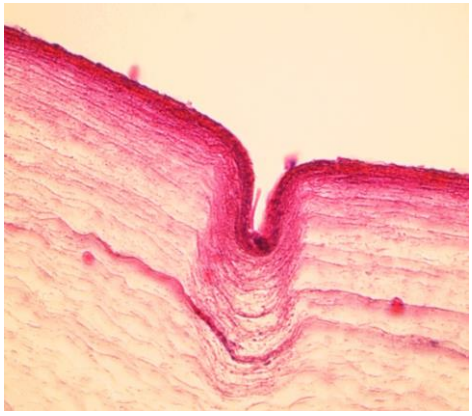
The TGF-family is the bridge between DHT and the activation of the caspase cascade. In recent studies, researchers have found DHT to promote TGF, and TGF to cause activation of the caspase cascade and thus, hair cell death, which clinically manifests as male and female pattern baldness. Studies with finasteride, a compound approved to treat AGA, suggest that hair loss prevention by this compound involves the blocking of caspase activation, especially caspase 3. The first triggers to prevent may be DHT damage or oxidative (free radical) stress on the mitochondria, TGF induction from DHT, TNF-alpha induction from allergic inflammation, or PKC upregulation by caspase activation.

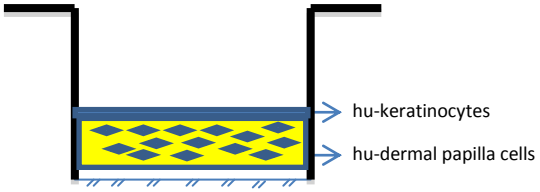
All these growth regulatory factors and intracellular pathways represent novel and interesting molecular targets to study the effects on novel products on hair physiology, hair growth and against hair loss.

PARAMETERS

The aim of this project is to test preparations of natural products (herbal extracts, fractions, compounds) in specific end-points on hair growth and the prevention of hair loss.

- Effects on the proliferation of dermal papilla cells
- Effects on various growth factors in dermal papilla cells (TGF, KGF, IGF, PDGF etc.)
- Effects on caspase-3, 7 and 9 in dermal papilla cells
- Effects on cellular energy levels (ATP) in dermal papilla cells/keratinocytes/fibroblasts
- Effects on VEGF expression in keratinocytes
- Effects on TERT
- Effects on 5-alpha reductase I and II
- Effects on Wnt/β-catenin pathway
- Effects on inflammation (TNFalpha, IL-1beta, IL-6)
- Effects on human dermal papilla cells/keratinocytes co-cultures/3D culture (all parameters)
- Other parameters on request





Contact:

Dr. Bernd L. Fiebich
VivaCell Biotechnology GmbH
Ferdinand-Porsche Str. 5
D-79211 Denzlingen
Phone: +49-761-4760502
Fax +49-761-4770946
www.vivacell.de
fiebich@vivacell.de
mobile +491792115187