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Trichology

Editor-in-Chief
BS Chandrashekar

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Section 1 Basic Trichology

ARTICLE 1

An Analysis of Gene Expression Data Involving Examination of Signaling Pathways Activation Reveals New Insights into the Mechanism of Action of Minoxidil Topical Foam in Men with Androgenetic Alopecia

Stamatas GN, Wu J, Pappas A, et al. An analysis of gene expression data involving examination of signaling pathways activation reveals new insights into the mechanism of action of minoxidil topical foam in men with androgenetic alopecia.
Cell Cycle. 2017;16(17):1578-84.

Abstract

Androgenetic alopecia (AGA) is the most common form of hair loss. Minoxidil has been approved for the treatment of hair loss; however its mechanism of action is still not fully clarified. In this study, we aimed to elucidate the effects of 5% minoxidil topical foam (MTF) on gene expression and activation of signaling pathways in vertex and frontal scalp of men with AGA. We identified regional variations in gene expression and perturbed signaling pathways using in silico Pathway Activation Network Decomposition Analysis (iPANDA) before and after treatment with minoxidil. Vertex and frontal scalp of patients showed a generally similar response to minoxidil. Both scalp regions showed upregulation of genes that encode keratin-associated proteins and downregulation of integrin-linked kinase (ILK), Akt and mitogen-activated protein kinase (MAPK) signaling pathways after minoxidil treatment. This study results provide new insights into the mechanism of action of minoxidil topical foam in men with AGA.

COMMENT

The pattern of hair loss in androgenetic alopecia (AGA) can be associated with various factors, such as the differences in the levels of hormone receptors and embryologic scalp patterning.

Topical minoxidil and oral finasteride have been approved by the Food and Drug Administration (USA) for the treatment of AGA. Minoxidil is an adenosine triphosphate (ATP) sensitive potassium (K^+) channel agonist as well as a vasodilator. Only one of two forms of K^+-ATP channels found in human hair follicles is sensitive to minoxidil. The drug's effect seems to be connected to its presence and stops when the treatment is discontinued.

Scalp biopsies from the frontal and vertex scalp were done from the leading edge of

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alopecia and global hair photographs were taken before and after 8 weeks of treatment. Based on a blinded review of stereotactic photographs, patients were categorized as having either full or minimal clinical response. Microarray analysis was done using the Affymetrix GeneChip HG U133 plus 2.0. Pathway activation analysis was performed using in silico Pathway Activation Network Decomposition Analysis (iPANDA).

The analysis revealed that both genes and noncoding RNAs were differentially expressed between vertex and frontal scalp before and after treatment with MTF 5%.

Variations in gene expression in the two scalp regions before treatment were observed. Several genes, including genes induced by oxidative stress and growth factors (*DUSP1* and *CYR61*) and noncoding RNAs, were upregulated in frontal compared to vertex scalp, while the expression of pseudogene *MSL3P1* that may be involved in chromatin remodeling and regulation of transcription was decreased. These results suggest that gene expression in hair follicles in vertex versus frontal scalp of patients with AGA may not be completely identical and exhibit different molecular signatures.

In general, vertex and frontal scalp showed similar molecular response to MTF 5% treatment. The strong upregulation of keratin-associated genes in both the vertex and frontal regions was a distinctive feature of responding patients, while patients who showed minimal response to MTF 5% treatment did not exhibit a similar level of upregulation of keratin-associated genes. The expression of several noncoding RNAs was significantly decreased in both scalp regions after treatment. It should be noted that keratinization-related genes were downregulated in the frontal scalp of both responders and placebo control patients. Thus, it is not clear whether the decreased expression of late cornified envelope protein 3D (LCE3D) was caused by the MTF 5% treatment or other as yet unidentified factors.

Baseline regional variations between frontal and vertex scalp were also visible upon pathway level examination. Thus, interleukin 2 (IL-2), which is being studied in the context of alopecia areata and integrin-linked kinase (ILK), a key mediator in integrin signal transduction, were upregulated pathways identified in frontal compared to vertex scalp. The following pathways were also upregulated in frontal versus vertex scalp before treatment—Mitogen-activated protein kinase (MAPK) (facilitates the survival of dermal papilla cells), transforming growth factor β (TGF-β) (induces catagen), Janus kinase/signal transducers and activators of transcription (JAK/STAT) (prevents anagen re-entry), phosphatase and tensin homolog (PTEN) and Akt (promotes dermal papilla cells survival and anagen initiation). The downregulated pathways included IL-6), which may provoke inflammation, and Presenilin action in Notch and Wnt signaling (NCI) pathways. It has been shown that activation of Notch signaling is necessary for keratinocyte differentiation, and Wnt signaling drives hair follicle morphogenesis, hair shaft differentiation, hair cycling induction, and maintenance.

The ILK, Akt and MAPK pathways became downregulated in both vertex and frontal scalp of responders after treatment with minoxidil topical foam (MTF) 5%.

The JAK/STAT signaling and Ras pathways were downregulated in vertex scalp of patients who responded to MTF 5% treatment. JAK/STAT inhibition should promote hair growth, while Ras pathway regulates cellular proliferation, differentiation, and senescence

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by stimulating various parallel effector pathways.

Protein digestion and absorption pathway, which includes several collagen-encoding genes, was significantly upregulated in the frontal scalp of responders. MTF 5% treatment also caused upregulation of mechanistic target of rapamycin (mTOR) pathway in the frontal scalp region. It is known that mTOR pathway promotes hair follicle stem cells proliferation and activation, and is activated at the moment of telogen-to-anagen transition.

Key Messages

- ***Vertex and frontal scalp of patients showed a generally similar response to minoxidil***
- ***Both scalp regions showed upregulation of genes that encode keratin-associated proteins and downregulation of ILK, Akt and MAPK signaling pathways after minoxidil treatment***
- ***Global response for minoxidil therapy in patterned hair loss is around 42–48%, according to many reports and studies. One of the research could be deficiency or absence or variation in K^+ (ATP) channel pathways and upregulation of gene expressions***
- ***Also to be noted from this study that minoxidil response is uniform across the scalp***
- ***Minoxidil upregulates gene expression to proliferate keratinocyte production and migration, and downregulates certain other gene expressions to reduce inflammation.***

ARTICLE 2

Development and Evaluation of Finasteride Loaded Ethosomes for Targeting to the Pilosebaceous Unit

Wilson V, Siram K, Rajendran S, et al. Development and evaluation of finasteride loaded ethosomes for targeting to the pilosebaceous unit.
Artif Cells Nanomed Biotechnol. 2018;46(8):1892-901.

Abstract

Androgenetic alopecia, a major cause for baldness, is caused by the deposition of dihydrotestosterone (DHT) at the androgen receptors present in the pilosebaceous unit (PSU). Finasteride (FIN) is a potent 5α-reductase inhibitor capable of preventing the conversion of testosterone to DHT. But, its oral administration in males is reported to have some sexual side effects. An attempt was made to prepare ethosomes of FIN with a size range 100–300 nm to enhance its delivery to the PSU. Finasteride loaded ethosomes (FES) were prepared using an ultra-probe sonicator and characterized for its size, morphology, surface charge and entrapment efficiency. The ability of FES to permeate across rat skin and frontal scalp skin of human cadaver was also evaluated. The spherical shaped ethosomes of different batches were in the size range of 107.8 ± 2.50 nm to 220.4 ± 6.92 nm and showed good permeation across rat skin and frontal scalp skin of human

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cadaver when compared to the unencapsulated FIN. The results portrayed the ability of FES to permeate across the stratum corneum to reach the PSU of the hair follicle. Although additional use of permeation enhancer increases the permeation of FIN across the skin, its addition may not be a favorable option for the deposition of ethosomes in the PSU.

COMMENT

Finasteride (FIN) is a 5α-reductase inhibitor and targeting it directly is beneficial. Ethosomes are a proven lipid-based nanocarrier to target compounds specifically to the pilosebaceous unit (PSU); the small size, vesicular nature of the ethosomes with ethanol and phospholipids boosts the permeation of the drugs and when used to target FIN at hair follicles, with permeation enhancers like oleic acid, thymol and isopropyl myristate may be beneficial in hair loss. The study attempts to evaluate this action and role of ethosomes. Substrates used are FIN, soya phosphatidylcholine (SPC), Rhodamine Red (RR), oleic acid, thymol, ethanol, isopropyl myristate and propylene glycol. A cold method was used to prepare FES; the average size, zeta potential and polydispersity index of the ethosomes were done using a Malvern Zetasizer (Nano ZS90, Malvern instruments, Malvern, Worcestershire) at 25°C. Finasteride loaded ethosomes (FES) were visualized under scanning electron microscopy (SEM) and atomic force microscopy (AFM), morphology were assessed, later entrapment efficiency was calculated using ultraviolet spectroscopy at 219 nm. In vitro release studies of FIN from FES were done at HiMedia Laboratories, Mumbai, India using dialysis membrane.

The permeation of FES was assessed using freshly excised dorsal skin from a sacrificed male Wistar rat; surface area 2 cm^2 was mounted in the Franz diffusion cell, receptor compartment was filled with 15 mL of pH 7.4 phosphate buffer saline (PBS), maintained at 37 ± 1°C and 1 mL of FES was applied, the amount of FIN present in the receptor chamber was analyzed by ultra-visible spectroscopy at 219 nm. Similarly, permeation of FES across the frontal scalp skin isolated from human cadaver was done using Franz diffusion cell as above, the cumulative percentage of FIN permeated per unit area was plotted as a function of time and the flux values were calculated from the slope and evaluating amount of FIN by spectroscopy. Depth and mechanism by which ethosomes loaded with a fluorescent probe (RR) penetrate the skin were studied in fluorescence microscopy.

Nine formulations were prepared by varying the amounts of SPC and ethanol; additional three formulations were prepared by adding three permeation enhancers. The particle size of FES ranged from 107.8 ± 2.50 nm to 220.4 ± 6.92 nm; when the amount of SPC was constant, an increase in the amount of ethanol from 10% to 30% significantly decreased ($p < 0.05$) the particle size of FES and increased entrapment efficiency. On the contrary, when the amount of ethanol was constant, an increase in the amount of SPC significantly increased ($p < 0.05$) the particle size of FES and reduced the amount of FIN entrapped in the ethosomes. A mild increase in the particle size was seen in all the formulations (FES 10, FES 11 and FES 12)

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with addition of permeation enhancer. The zeta potential of polyethersulfone (PES) were almost neutral the values ranging from –1.45 ± 0.84 mV to –11.8 ± 2.65 mV. Three dimensional micrographs obtained from SEM showed individual unilamellar vesicles with smooth spherical morphology and the size of the vesicles concordance with the values obtained by DLS readings. Entrapment efficiency ranged 88.4 ± 3.56% to 62.9 ± 2.15% affected by amount of ethanol and SPC; highest entrapment efficiency was observed for formulation FES3 containing 30% ethanol and 2% propylene glycol. Addition of permeation enhancer also influenced the amount of FIN entrapped in the ethosomes and entrapment efficiency except thymol. Thus, high entrapment efficiency is obtained by high amount of ethanol, low amount of SPC and a lipophilic permeation enhancer.

The release of FIN followed diffusion and erosion-controlled model with biphasic release pattern ($p < 0.05$) for all the formulations and 25% of FIN was released in the initial phase with sustained pattern of release of FIN from FES for about 8 hours. The cumulative amount of FIN permeated across the rat skin was significantly higher ($p < 0.05$) for FIN when it is encapsulated in ethosomes when compared to its free form (FIN-PBS); Transdermal flux of the formulations were in the range of 67.36 ± 9.23 to 47.92 ± 8.21 $\mu g/cm^2/h$, whereas a significantly ($p < 0.05$) lower transdermal flux (39.29 ± 10.3 $\mu g/cm^2/h$) was observed for FIN-PBS. In human skin, FES10 containing oleic acid showed highest transdermal flux of 48.66 ± 7.24 $mg/cm^2/h$ followed by 38.47 ± 3.56 $mg/cm^2/h$ and 33.16 ± 5.93 $mg/cm^2/h$ for formulations FES12 and FES11 containing IPM and thymol, respectively. Human scalp skin is comparatively thicker than the rat skin; the amount of FES penetrated over a period of 8 hours across frontal scalp skin of a human cadaver was low when compared to the rat skin.

Fluorescent intensity obtained after application of RES was significantly ($p < 0.05$) higher than the fluorescent intensity observed after application of RR-PBS and RRET. Thus, drugs or molecules encapsulated in ethosomes would show better penetration, however, storage of ethosomes at refrigerated conditions to be considered to maintain stability.

Key Messages

- ***Ethosomes of various other drugs meant for topical application would be a good option to enhance permeation to and across the skin***
- ***This research paper on ethosomes carrying active drug into the PSU units a novel experiment with high precision and appears to be a milestone in drug penetration enhancer category; ethosomes carry drugs across the skin irrespective of PSU. FIN which is trapped in ethosomes gets diffused in to the circulation which is not a target delivery. The experiments have to be made in developing penetration enhancer and dry trap molecules which enter only PSU, so that systemic side effects of FIN are brought to nil.***

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ARTICLE 3

The Effect of Plasma Rich in Growth Factors Combined with Follicular Unit Extraction Surgery for the Treatment of Hair Loss: A Pilot Study

Navarro RM, Pino A, Martinez-Andres A, et al. The effect of plasma rich in growth factors combined with follicular unit extraction surgery for the treatment of hair loss: A pilot study.
J Cosmet Dermatol. 2018;17(5):862-73.

Abstract

Androgenetic alopecia (AGA) is one of the most common dermatological problems encountered in day-to-day practice. Among the various treatment modalities available, only topical minoxidil and oral finasteride are Food and Drug Administration (FDA) approved. Though plasma rich in growth factors (PRGFs) technology has emerged as a promising therapeutic modality in the management of AGA and adjuvant in hair transplantation surgery, there are no well-established evidence for its recommendation. The aim of this study was to evaluate the safety and clinical efficacy of PRGF technology as an adjuvant therapy for follicular unit extraction (FUE) surgery in hair loss affected patients.

COMMENT

Plasma rich in growth factors technology is based on the recovery of a small volume of the patient's own blood which is afterward centrifuged and activated to obtain an autologous formulation enriched in proteins and growth factors. The study involved three in vitro tests and one in vivo study to evaluate the efficacy of PRGF both at cellular level and clinical response. In vitro studies included cell culture and characterization, cell proliferation, and cell migration studies. The prepared PRGF reached 2.29 platelet enrichment over the peripheral blood in in vitro studies and with significant high levels of several key growth factors for hair follicle regeneration like TGFb1, PDGF-AB, EGF, VEGF, IGF, FGFb and HGF.

In cell culture and characterization, the two human follicular phenotypes, germinal matrix cells (GMCs) and dermal papilla cells (DPCs) were cultured in a suitable medium [humidified atmosphere at 37°C with 5% CO_2 with mesenchymal stem cell medium (MSCM)] and the fibroblast-like morphology of cells checked by phase-contrast microscopy showed that both cell types showed spindle-shaped appearance and fibroblast-like elongation. The cells were uniformly positive for standard fibroblast markers collagen type I, fibronectin, and vimentin while showed negative for endothelial P-cytokeratin marker which was confirmed by immunofluorescence microscopy.

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Germinal matrix cells and DPC were plated at high density in 96-well optical bottom black culture plates and cultured for 72 hours with culture medium supplemented with 0.2% (v/v) FBS (as a control of nonstimulation) or FBS/MSCGS-free culture medium supplemented with 20% (v/v) PRGF in cell proliferation study. Results showed that PRGF-treated group had high DNA concentration compared to nontreated one ($p < 0.05$). The analysis of migratory activity of follicular cells in response to PRGF showed migration of fibroblasts into the empty gap area between opposite cell frontlines which was statistically significant when compared to controls ($p < 0.05$).

In a clinical study involving 30 hair transplantation, in clinically diagnosed AGA for FUE hair transplant surgery. They were randomized into two groups such that 15 patients received the conventional FUE surgery (control group) while the remaining 15 subjects underwent FUE surgery plus PRGF treatment.

Histomorphometric evaluation (H&E-stained cross-sections) showed the growth factor-rich fibrin preserved pilosebaceous unit along with its associated structures including sebaceous and sweat glands, arrector pili muscle, and bulge region in PRGF-preserved grafts. The immunofluorescent images showed that the scaffold provides a natural source of growth factors (PDGF) that adhere to the clot–graft interface and may even penetrate into the FTU before being reimplanted into the receptor area. PRGF-preserved grafts ($p < 0.05$) had high proliferative epidermal cells. The immunofluorescence analysis revealed a significantly higher PDGF-weighted fluorescence (WF) detected in the dermis of the PRGF-preserved FTUs ($p < 0.05$) although there were no statistical differences observed between PDGF-WF at the epidermal layer.

Hematoxylin and eosin-stained FTUs showed that there was significant reduction in the structures associated to the follicular unit (such as sebaceous glands, sweat glands, or the arrector pili muscle) and interstitial edema ($p < 0.05$) in PRGF-samples, whereas the 75% of the control samples were found to be seriously impaired. Transected FTUs were analyzed for preservation of the perifollicular collagen. Results showed that PRGF-preserved FTUs presented a higher amount of collagen compared to control grafts ($p < 0.05$). The structural fiber organization in terms of damaged/healthy collagen percentage was also improved after PRGF treatment compared to the one detected in control samples ($p < 0.05$). The orcein stain was used to analyze the elastic fiber. Results showed that the elastic fiber integrity in PRGF-preserved FTUs, 44% of them did not show and 52% showed slight impairment of elastic fiber compared to control sample which was slightly (62%) or seriously (38%) impaired.

Patients were clinically assessed 24 hours and several days after the conventional FUE surgery (control group) or FUE + PRGF treatment (PRGF group). Faster postsurgical crust healing and hair fixation was noticed in PRGF during FUE surgery compared to the control group ($p < 0.05$). The postsurgical inflammation period was also significantly reduced by means of scalp pain, itching and redness decrease in PRGF group ($p < 0.05$). One-year follow-up visits revealed an optimal hair retention status in patients subjected to either FUE or FUE + PRGF intervention. The limitation of study is short follow-up, small sample size, and also needs phototrichogram which would have been more authentic in comparing the control versus cases.

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Key Messages

- ***Plasma rich in growth factors technology is emerging as an important adjuvant in the management of AGA***
- ***It has been shown, in both in vitro and in vivo studies, that the platelet-derived growth factors have significant role in germinal matrix and dermal papilla cell proliferation and also when added to hair transplantation, these provide better collagen and elastin network, early follicle take up, and quick postoperative recovery.***

ARTICLE 4

Therapeutic Potential of Stem Cells in Follicle Regeneration

Owczarczyk-Saczonek A, Krajewska-Włodarczyk M, Kruszewska A, et al. Therapeutic potential of stem cells in follicle regeneration.
Stem Cells Int. 2018;2018.

Abstract

Alopecia is caused by a variety of factors which affect the hair cycle and decrease stem cell activity and hair follicle regeneration capability. This process causes lower self-acceptance, which may result in depression and anxiety. However, an early onset of androgenic alopecia is associated with an increased incidence of the metabolic syndrome and an increased risk of the cardiac ischemic disease. The ubiquity of alopecia provides an encouragement to seek new, more effective therapies aimed at hair follicle regeneration and neoregeneration. We know that stem cells can be used to regenerate hair in several therapeutic strategies—reversing the pathological mechanisms which contribute to hair loss, regeneration of complete hair follicles from their parts, and neogenesis of hair follicles from a stem cell culture with isolated cells or tissue engineering. Hair transplant has become a conventional treatment technique in androgenic alopecia (micrograft). Although an autologous transplant is regarded as the gold standard, its usability is limited, because of both a limited amount of material and a reduced viability of cells obtained in this way. The new therapeutic options are adipose-derived stem cells and stem cells from Wharton's jelly. They seem an ideal cell population for use in regenerative medicine because of the absence of immunogenic properties and their ease of obtainment, multipotential character, ease of differentiating into various cell lines, and considerable potential for angiogenesis. In this article, we presented advantages and limitations of using these types of cells in alopecia treatment.

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COMMENT

Hair follicular stem cells (HFSCs) form niche for mature stem cells in the hair follicles (HFs). There are variety of factors which affect the hair cycle, leading to decreased stem cell activity and HF regeneration capability, causing alopecia. Dermal papilla cells (DPCs) play an important role in induction and regulation of hair growth and the formation of new HFs. Signals from DPCs activate stem cells in the "bulge" and germinal matrix cells in the late telogen/early anagen phase by activating the Wnt/β-catenin pathway. Alopecia involves changes in both HFSCs and DPCs.

In scarring alopecia, inflammatory cell infiltration around the bulge results in an irreversible loss of HFSCs. Patchy and androgenic alopecia are reversible as the progenitor cells are damaged, but the HFSCs are preserved. CK15+ or CD34+ cells have been identified as "bulge" cells. Stem cells of the upper and lower parts of the bulge in the telogen HF affect the expression of CD34. Cells participating in the formation of a new anagen hair express Lgr5, but not CD34.

Immunoreactivity of CK15 is reduced in patients with patchy alopecia, but is present in androgenic alopecia. There is a decrease in hair follicular CD34 levels in the frontal parts of the scalp, whereas its expression is well preserved in occipital region hair follicles. In patchy alopecia, there is poor expression of CD200 of matrix cells, which is a sign of disappearance of the immune privilege.

The new therapeutic approaches in the treatment of alopecia are stem cells derived from adipose tissue and Wharton's jelly derived stem cells, due to the absence of immunogenic properties and multipotent character, ease of obtainment, and differentiating into various cell lines, and the potential for angiogenesis. This seems as ideal cell population for use in regenerative medicine.

Knowing the mechanism of activation of multipotent stem cells allows their use in regenerative medicine. The effect of microenvironment and expression of receptors on different growth factors complicates its use, and not all stem cell therapy target points have been identified.

Key Messages

- ***The new therapeutic approaches in the treatment of alopecia are stem cells derived from adipose tissue and Wharton's jelly derived stem cells***
- ***Adipose-derived stem cells seem an ideal cell population for use in regenerative medicine, due to absence of immunogenic properties and multipotent character, ease of obtainment and differentiating into various cell lines, and the potential for angiogenesis***
- ***Due to its noninvasive and painless acquisition, ready availability from a large pool of donors, no ethical limitations, no risk to the donor, high multipotential differentiation capability and weak immunogenic potential, Wharton's jelly has become a preferential source of stem cells. Cells can be obtained with an expression of hair-like structures and cytokeratin 19 (CK19) under in vitro conditions. Self-regeneration potential of modified skin is determined by CK19, a marker of bulge stem cells***
- ***Tissue homeostasis and damage repair is necessary in maintaining a pool of stem cells.***

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ARTICLE 5

Epithelial-to-Mesenchymal Stem Cell Transition in a Human Organ: Lessons from Lichen Planopilaris

Imanishi H, Ansell DM, Chéret J, et al. Epithelial-to-Mesenchymal Stem Cell Transition in a Human Organ: Lessons from Lichen Planopilaris.
J Invest Dermatol. 2018;138(3):511-9.

Abstract

Dissecting cellulitis is a disease of skin with inflammatory origin. The case reported here is of a patient of Crohn's disease with recurrent dissecting cellulitis. A 31-year-old man with purulent scalp lesions presented with abdominal pain, hematochezia, weight loss and night sweats. A diffuse friable mucosa with extensive pseudopolyps was seen on colonoscopy. Scalp biopsy showed epidermoid inclusion cysts with chronic inflammatory cell infiltration and granulation tissue, suggesting of dissecting cellulitis. The occurrence of Crohn's disease with dissecting cellulitis is under reported. Dissecting cellulitis of scalp has a tendency to recur, and considering an underlying condition of this nature is the key for its appropriate management.

COMMENT

Epithelial-to-mesenchymal transition (EMT) is a physiological feature of embryogenesis and wound healing. EMT occurs in pathological processes such as malignant transformation of epithelial cells, metastasis and several fibrotic diseases. It occurs in the bulge of hair follicles (HFs) in inflammatory alopecia like lichen planopilaris (LPP). This study aims at exploring whether human scalp HFs can serve as an instructive model system for studying the EMT process in epithelial stem cells (eSCs) in live human tissue. It also portrays that eSCs in the HF bulge undergo EMT in LPP and that this process may be experimentally induced even in healthy human bulge eSC ex vivo, if exposed to appropriate EMT-promoting stimuli.

In this study, patients with LPP and healthy controls were considered. Lesional skin was obtained from clinically inflamed edges of alopecia; even nonlesional skin was obtained from the patients of LPP. The specimen from the healthy controls was obtained from the occipital scalp. Quantitative real-time polymerase chain reaction (RT-PCR), human hair follicle organ culture, culture of LPP tissue and outer root sheath keratinocyte cells, immunohistochemistry and quantitative immunohistomorphometry and transmission electron microscopy were done.

The authors concluded LPP to be a model disease for pathological EMT in human adult eSCs. EMT signature can be induced and manipulated in human eSCs with peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists.

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Key Messages

- ***Lesional LPP HFs display morphological and ultrastructural signs of EMT within their eSC niche***
- ***Lichen planopilaris bulge epithelium shows an mRNA and protein signature compatible with the occurrence of EMT***
- ***Cells undergoing EMT within the bulge express the eSC marker Keratin 15+***
- ***Epithelial-to-mesenchymal transition can be induced in healthy human HF's ex vivo***
- ***Pioglitazone stimulates PPAR-γ via downregulation of transforming growth factor-beta (TGF-β), protecting against and partially reversing EMT induction***
- ***The PPAR-γ stimulation by N-acetyl-GED partially reverses EMT signature in normal and LPP HFs.***

ARTICLE 6

The Unusual Reproductive System of Head and Body Lice (*Pediculus humanus*)

De la Filia AG, Andrewes S, Clark JM, et al. The unusual reproductive system of head and body lice (*Pediculus humanus*). ***Med Vet Entomol. 2018;32(2):226-34.***

Abstract

Insect reproduction is extremely variable, but the implications of alternative genetic systems are often overlooked in studies on the evolution of insecticide resistance. Both ecotypes of *Pediculus humanus* (Phthiraptera: Pediculidae), the human head and body lice, are human ectoparasites, the control of which is challenged by the recent spread of resistance alleles. The present study conclusively establishes for the first time that both head and body lice reproduce through paternal genome elimination (PGE), an unusual genetic system in which males transmit only their maternally derived chromosomes. Here, we investigate inheritance patterns of parental genomes using a genotyping approach across families of both ecotypes and show that heterozygous males exclusively or preferentially pass on one allele only, whereas females transmit both in a Mendelian fashion. We do however observe occasional transmission of paternal chromosomes through males, representing the first known case of PGE in which whole-genome meiotic drive is incomplete. Finally, we discuss the potential implications of this finding for the evolution of resistance and invite the development of new theoretical models of how this knowledge might contribute to increasing the success of pediculicide-based management schemes.

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COMMENT

Pediculus humanus is a blood-sucking ectoparasite, the two ecotypes—*Pediculus humanus capitis* and *Pediculus humanus* differ in their ecology and clinically. The allele transmission in females followed Mendelian expectations, it was non-Mendelian in males: heterozygous male parents systematically passed on one of their two alleles to their offspring. In this study, the authors try to conclusively establish that both head and body lice reproduce through paternal genome elimination (PGE), an unusual genetic system in which males transmit only their maternally derived chromosomes.

In this study, a series of intraspecific crosses was set up using individuals from the head louse strain SF-HL and the body louse strain Frisco-BL. Approximately 50 males and 50 females were used to temporarily establish a colony and approximately 30–50 eggs were introduced each time. Both colonies have been maintained by the Clark Laboratory at the University of Massachusetts Amherst on human blood using the same in vitro rearing system. Offspring (F1) of all crosses were raised until early third instar stage and then transferred to ethanol. Total genomic DNA from parents and body louse F1 individuals was extracted and polymerase chain reaction (PCR) was performed and upon reception of raw trace files, microsatellite alleles were scored using the microsatellite plugin.

This study shows conclusive evidence of a genome-wide male transmission ratio distortion in both ecotypes of *P. humanus*: males exclusively transmit only one of their alleles to their offspring. The heterozygous genotypes in males from both ecotypes unambiguously indicate that males are diploid and that both paternally and maternally inherited chromosomes are kept in the soma. All males in the present study exhibited whole-genome transmission ratio distortion with sporadic, inconsistent leakages of nondriving alleles in some individuals. Allele transmission patterns in louse males reveal that paternal chromosomes are similarly excluded from active spermatocytes, but are occasionally able to escape elimination by migrating with other maternal chromosomes in lieu of their homologues, particularly in body lice. The authors observe occasional transmission of paternal chromosomes through males, representing the first known case of PGE in which whole-genome meiotic drive is incomplete and discuss the potential implications of this finding for the evolution of resistance and invite the development of new theoretical models of how this knowledge might contribute to increase the success of pediculicide-based management schemes.

Paternal genome elimination is present in both *P. humanus* ecotypes and this study outlines some considerations of the impact of the particular genetic system on the evolution of pediculicide resistance. The characterization and compact nature of the *P. humanus* genome enables genome-wide allele-specific expression studies to determine the extent to which paternally inherited alleles can confer resistance phenotypes in male.

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