REVIEW ARTICLE

Prostanoids and Hair Follicles: Implications for Therapy of Hair Disorders

Xue-Gang XU and Hong-Duo CHEN
Department of Dermatology, No. 1 Hospital of China Medical University, Shenyang, China

Prostanoids, including prostaglandins (PGs) and thromboxane A_2 (TXA_2), are a family of lipid-derived autacoids that modulate many physiological systems and pathological contexts. Prostanoids are generated by sequential metabolism of arachidonic acid, catalysed by cyclo-oxygenase, to PGH2, which is then converted to PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and TXA_2, catalysed by their specific synthases. Recent evidence suggests that prostanoids play a role in regulating hair growth. The $PGF_{2\alpha}$ analogue is Food and Drug Administration-approved in the US and routinely used to enhance the growth of human eyelashes. PGE_2 is reported to protect from radiation-induced hair loss in mice. Conversely, PGD_2 inhibits hair growth. This paper reviews the metabolism of prostanoids and the expression pattern of prostanoid receptors in hair follicles, focussing on their different and opposing effects on hair growth and the underlying mechanisms. This has potential clinical relevance in the treatment and prevention of hair disorders.

Key words: prostanoid; prostaglandin receptor; PGF2α analogue; hair follicle.

Accepted Nov 13, 2017; Epub ahead of print Nov 14, 2017

Acta Derm Venereol 2018; 98: 318–323.

Corr: Hong-Duo Chen, Department of Dermatology, No. 1 Hospital of China Medical University, Shenyang 110001 China. E-mail: hongduochen@hotmail.com

Prostaglandins (PGs) and thromboxane A_2 (TXA_2) are termed prostanoids and are derived from arachidonic acid and other long-chain polyunsaturated fatty acids (1). The biosynthesis of prostanoids begins with the release of arachidonic acid from the plasma membrane of cells by phospholipases (PLAs), following metabolism via the sequential actions of cyclo-oxygenase (COX) and respective synthases. Prostanoids modulate many physiological systems, including the immune, respiratory, gastrointestinal, cardiovascular, and genitourinary systems (1, 2). Research on prostanoids has focused on inflammation and inflammatory responses, and the relationship between prostanoids and hair follicles has been investigated largely through adverse events and case reports (3, 4). This review discusses the biosynthesis of prostanoids and their metabolism in hair follicles, with particular regard to advances in research into prostanoids and hair follicle growth, hair follicle cycle, and hair disorders.

PROSTANOID METABOLISM

There are 2 main COX isoforms, COX-1 and COX-2, both of which can transform arachidonic acid into PGH2. COX-1 is constitutively expressed, while COX-2 is induced by mitogenic and pro-inflammatory stimuli. PGH_2 is then transformed into different PGs and TXA_2, catalysed by different synthases. The mainly bioactive prostanoids generated *in vivo* include PGE_2, PGI_2, PGD_2, $PGF_{2\alpha}$, and TXA_2. TXA_2 is characterized as modulating haemodynamics and cardiovascular functions; therefore this review focusses on other PGs. Prostanoids act as autocrine/paracrine local hormones through specific G-protein-coupled receptors. The 5 types of prostanoids, PGE_2, PGI_2, PGD_2, $PGF_{2\alpha}$, and TXA_2, bind to PGE_2 receptors (EP_1, EP_2, EP_3, EP_4), PGI_2 receptor (IP), PGD_2 receptors (DP_1, DP_2), $PGF_{2\alpha}$ receptor (FP), and thromboxane A_2 receptor (TP) respectively (**Fig. 1**). Different prostanoids have different, or even opposing, properties, possibly due to the fact that they bind to different receptors and

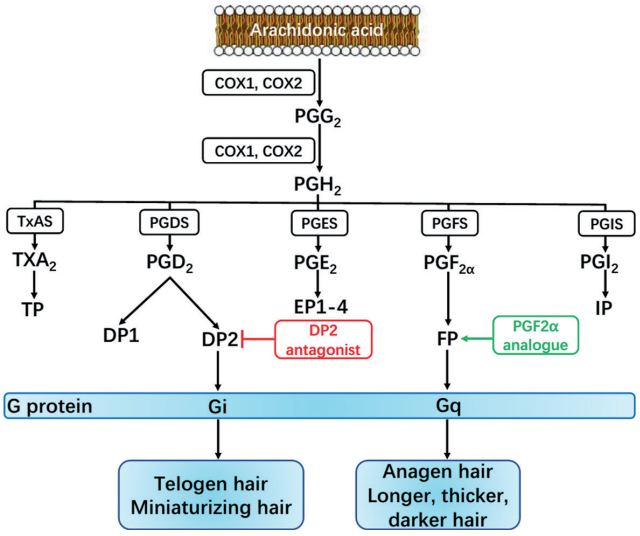

Fig. 1. Schematic of the biosynthesis of prostanoids and their biological effects on hair follicles via activating different cell surface G protein-coupled receptors. Different prostanoids can bind different receptors and G-protein, trigger different second messengers and lead to different effects to hair follicles. $PDF_{2\alpha}$ analogues can activate FP. DP2 antagonists can inhibit DP2 activation. All have treatment potential for hair loss. COX1: cyclo-oxygenase 1; COX2: cyclo-oxygenase 2; PGG_2: prostaglandin G_2; PGH_2: prostaglandin H_2; TxAS: TXA_2 synthase; PGDS: PGD_2 synthase; PGES: PGE_2 synthase; PGFS: $PGF_{2\alpha}$ synthase; PGIS: PGI_2 synthase; TXA_2: thromboxane A_2; PGD_2: prostaglandin D_2; PGE_2: prostaglandin E_2; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$; PGI_2: prostaglandin I_2; TP: TXA_2 receptor; DP1: PGD_2 receptor 1; DP_2: PGD_2 receptor 2; EP: PGE_2 receptor; FP: $PGF_{2\alpha}$ receptor; IP: PGI_2 receptor.

doi: 10.2340/00015555-2843
Acta Derm Venereol 2018; 98: 318–323

Table I. Expression pattern and signal transduction of prostaglandin (PG) receptors

Class	Subtype	Expression pattern	G-protein-coupled	Second messenger
PGD_2	DP1	Basal layer of epidermis (+/–) hair follicle ORS (+)	Gs	cAMP↑, Ca^{2+}↑
	DP2	All epithelial compartments of epidermis and hair follicle (+/–)	Gi	cAMP↓, Ca^{2+}↑
PGE_2	EP1	Basal cells of epidermis (+), hair follicles (+), DP (++)	Gq	IP_3/DAG/Ca^{2+}↑
	EP2	Epidermis (+, perinuclear expression), hair follicles (+), DP (++)	Gs	cAMP↑
	EP3	Epidermis (+, nuclear expression), hair follicles (+), DP (++)	Gi, G12	cAMP↓, Ca^{2+}↑, Rho
	EP4	Epidermis (+, cytoplasmic expression), hair follicles (+), DP (+/–)	Gs	cAMP↑
PGI_2	IP	hair shaft cuticle cells (+), epidermis (+/–)	Gs	cAMP↑
$PGF_{2\alpha}$	FP	Epidermis (–), most hair compartments (+)	Gq	IP_3/DAG/Ca^{2+}↑, Rho

DP: dermal papilla; IRS: inner root sheath; ORS: outer root sheath.

have different signalling pathways induction (**Table I**) (5). This review focusses mainly on PGD_2 and $PGF_{2\alpha}$, which are more closely related to hair growth.

There are 2 PGD_2 synthases, lipocalin PGDS (L-PGDS) and haematopoietic PGDS (H-PGDS). These differ biochemically with respect to features such as sequence, structure, cellular localization and tissue distribution (6). PGD_2 can bind and activate 2 distinct receptors, DP1 and DP2 (2). DP1 triggers Gs-type G-protein-coupled adenylate cyclase, which increases intracellular cAMP and calcium flux. DP2 triggers Gi-type G protein, which leads to inhibition of cAMP and calcium flux. PGD_2 can act as either a pro- or anti-inflammatory mediator, depending on the disease process and aetiology. The expression pattern of L-PGDS/H-PGDS and DP1/DP2 may account for different signalling pathway activation post-PGD_2 production. Unlike PGD_2, $PGF_{2\alpha}$ binds to a single receptor, FP. Activation of FP leads to G_q-type G protein mediated IP_3 generation and increased intracellular calcium flux (2). The FP receptor can also couple to the small G-protein Rho via a Gq-independent mechanism. However, in high concentrations, $PGF_{2\alpha}$ can also activate EP2. High concentration PGE_2 can activate FP and both the cross-activation of EP and FP can lead to COX-2 expression (1). Cross-talk between the FP and EGF receptor signalling and the β-catenin pathway has also been reported. The effects of prostanoids on these G-protein-coupled signalling pathways may also change as a function of ligand concentration or structure. These characteristics might explain their synergistic and/or antagonistic effects in many physiological systems and a broad array of diseases (Fig. 1).

HAIR FOLLICLE BIOLOGY

Anatomically, the hair follicle is an intricate mini-organ comprising epithelial and mesenchymal cells. The structure of hair follicles from outside to inside includes a fibrous connective tissue sheath, an outer root sheath, an inner root sheath, and the hair shaft (7). Together with the sebaceous gland and the arrector pili muscle, the hair follicle is part of the pilosebaceous unit. A rich blood supply flows to the hair follicles, and hair follicles are also richly innervated. In general, hair follicles can be divided into a permanent upper part and a transient lower cycling part, based on their differences during the hair cycle and their biological characteristics (8). The hair follicle cycle consists of stages of hair growth (anagen), follicle regression (catagen), rest (telogen), and hair shedding (exogen) (7, 9). The hair matrix and proximal outer root sheath (transient lower part) are degenerated by apoptosis during catagen. At the onset of anagen, bulge stem cells in the permanent part transiently produce their descendants, which actively proliferate and migrate to the lower part to regenerate the lower cycling part. The hair cycle in humans is asynchronous, which differs from many other mammals with synchronous hair cycles. Under physiological conditions, approximately 84% of the human scalp hair follicles are in anagen, 2% in catagen, and 14% in telogen, and 70–100 hairs are shed daily. The duration of the entire hair cycle depends on the location and type of hair follicle. The final length of hairs is proportional to the duration of anagen. For example, human eyebrow hair follicles and eyelash hair follicles are short because the anagen phase of hair follicles of eyebrow is only 2–4 weeks and the anagen phase of eyelash hair follicles is 1–4 months, while scalp follicles grow long because they stay in anagen for 2–6 years (10, 11). Except for rare congenital hair disorders and wound-induced "scarring" alopecia, most patients' hair disorders are related to aberrations in hair follicle cycling.

PROSTANOIDS AND PROSTANOID RECEPTORS IN HAIR FOLLICLES

In a mouse telogen skin model, COX-1 was the major isoform expressed in keratinocytes of the interfollicular epidermis and the upper part of the hair follicle, whereas COX-2 protein was barely detectable (12). Müller-Decker et al. (13) demonstrated that COX isozymes were spatiotemporally expressed during morphogenesis of mouse dorsal skin. COX-1 was detected in spinous and granular keratinocytes of the suprabasal compartment at E15–E18, and this pattern of expression was detected in skin through day 28 after birth, as well as in the skin of 7-week-old mice. Dendritic cells located interfollicularly and in the distal portion of the hair follicle of neonatal and adult skin were also COX-1 positive, which might indicate a role of COX-1 in the skin immune system. COX-2

appeared in all cells of elongated hair germs and hair pegs during hair morphogenesis. During the gradual transition of early stage hair follicles into fully differentiated follicles after birth, COX-2 expression became restricted to basal outer root sheath (ORS) and sebaceous gland cells (12). When follicles entered catagen, COX-2 expression declined, and was barely detectable in telogen follicles (12). As the key reaction in PG biosynthesis, COX-1 and COX-2 are spatiotemporally expressed during hair follicle morphogenesis and hair follicle cycling, which may contribute to PG production and hair follicle biology.

Several studies on prostanoid metabolism and prostanoid receptor distribution in human hair follicles have been reported (Table I). Colombe et al. (13) investigated the expression profile of key enzymes of PG metabolism in human hair follicles. Their experiments revealed that human hair follicles expressed mPGES-1, mPGES-2 and cPGES, which catalyse PGH_2 to PGE_2, as well as AKR1C3/PGFS, which converts PGH_2 to $PGF_{2\alpha}$ (13). These observations support the concept that PGs are involved in hair growth and differentiation control. Garza et al. (14) measured the expression level of *Ptgds* mRNA during hair cycles and found that *Ptgds* peaked in late anagen and was much higher than in telogen, similar to the expression pattern of fibroblast growth factor 5 (a known marker of catagen onset). They further discovered that PGD2 peaked after the apex of Ptgds expression. They claimed that Ptgds was first expressed in late anagen and PGD2 was produced via *Ptgds* during catagen, indicating that the PGD_2 pathway directly inducted the apoptotic catagen stage. Using immunohistochemistry techniques on mouse skin tissue, Ptgds was evident in late anagen in the keratinocytes of the ORS below the arrector pili muscle. In human hair follicles, a similar presence of PTGDS in the non-permanent region of hair follicles has been found (14).

All of the prostanoid receptors have been reported as present in hair follicles (5). Most of these receptors have shown a wide spectrum of expression in cultured cells and whole hair follicles (Table SI[1]). The expression of EP_2, EP_3, EP_4, DP_2, and TP and, to a lesser extent, EP_1, involved several hair follicle compartments (5). Conversely, IP and DP_1 were more specifically expressed in the hair cuticle layer and ORS basal layer, respectively (5). FP expression was restricted to the ORS companion layer and dermal papilla (5). Nesher et al. performed an immunohistological study of human eyelids, finding that FP was located predominantly in the inner root sheath of the bulb and stem of eyelashes and expressed only in eyelashes in the anagen phase (15). Therefore, the expression pattern of different prostanoid receptors may differ in different tissues or species. Although the exact functional significance of the expression of these prostanoid receptors remains unclear, it does explain some biological effects of some PGs, such as how FP expression in dermal papilla is related to the effect of PGF2α on hair growth. All these observations of prostanoids and prostanoid receptors support the idea that prostanoids are involved in hair biology.

PROSTAGLANDIN-INDUCED HAIR GROWTH

The potential role of PGs in the treatment of alopecia was first noted in the observation that eyelashes and eyebrows grew longer as a side effect following topical application of PG analogues in glaucoma treatment. Latanoprost was first documented as a hair-growth stimulant by Johnstone in 1997 (3). In 43 patients receiving unilateral topical latanoprost, hypertrichosis involved the ipsilateral terminal eyelashes and regional intermediate hairs of the upper and lower eyelid, as well as vellus hair of the lower eyelid skin. Increased hair numbers, length, thickness, curvature, and pigmentation were observed in the latanoprost-treated eye. Recently, a placebo-controlled trial in men with mild androgenetic alopecia (AGA) showed that the application of 0.1% latanoprost significantly increased hair density and pigmentation (16). Sixteen men with AGA (Hamilton-Norwood patterns of baldness II–III) were treated with 0.1% latanoprost and placebo on two mini-zones of the scalp. Compared with the baseline and placebo-treated sites, the latanoprost-treated sites showed increased hair density. Coronel-Pérez et al. conducted a survey of subjects with alopecia areata (AA) universalis treated with injections of triamcinolone acetonide and latanoprost 0.005% ophthalmic solution in their eyelid margins, and total or moderate responses were reported by 45% of subjects (17). However, Faghihi et al. and Ross EK et al. reported no efficacy of topical latanoprost in the treatment of eyelash and eyebrow AA (18, 19).

Bimatoprost is the only Food and Drug Administration (FDA) approved PGF2α analogue for the treatment of eyelash hypotrichosis (Fig. 1, Table SI[1]) (20–22). The efficacy and safety of bimatoprost in the treatment of eyelash hypotrichosis has been well documented, with clinical ratings, digital image analysis, and patient-reported measures of satisfaction (Table SI[1]) (23–26). A clinical study showed that, compared with latanoprost, the application of ophthalmic bimatoprost solution (0.03%) resulted in a higher occurrence of eyelash growth. A recent retrospective review of 585 subjects treated with 0.03% bimatoprost for eyelash hypotrichosis revealed a patient satisfaction level of 92.5%, and long-term use for at least 12 months was safe (25). Many clinical trials and observations have also reported the use of bimatoprost in other hair disorders, including thinning of the eyebrows, eyebrow hypotrichosis, and chemotherapy-induced hypotrichosis (Table SI[1]). One study showed that bimatoprost was equally efficacious as minoxidil in enhancement of eyebrow thickness, with fewer side-

[1]https://doi.org/10.2340/00015555-2843

effects (27). A multicentre, double-blinded, randomized, parallel-group study showed that daily treatment with bimatoprost ophthalmic solution 0.03% for 1 year was effective and well tolerated in patients with idiopathic and chemotherapy-induced eyelash hypotrichosis (28).

The efficacy and safety of topical bimatoprost for alopecia areata (AA) has been controversial or negative (29–31). A 1-year retrospective study indicated that 43.24% of patients with AA universalis achieved an acceptable cosmetic response with 0.03% bimatoprost (30). However, reports indicated no efficacy of bimatoprost in the treatment of AA. Roseborough et al. (32) enrolled 11 eyelash AA patients in a 16-week, randomized, investigator-masked, controlled study, which showed no significant changes in any patients. Borchert et al. (33) enrolled 71 adolescents with chemotherapy- or AA-induced eyelash hypotrichosis and healthy controls in a multicentre, randomized, double-masked, parallel-group study. Significant treatment benefits with bimatoprost vs. vehicle were evident among the healthy adolescents, but not in the post-chemotherapy or AA subgroups. Some authors have questioned whether these treatment failures were due to inadequate penetration of hair follicles without eyelashes, irreparable damage of follicle stem cells or too severe alopecia, among other reasons (31). However, these "positive" studies were uncontrolled or poorly controlled, and the controlled studies have been "negative". Therefore, more studies with a larger sample size, longer study duration, and higher concentration of medication are suggested to confirm whether $PGF_{2\alpha}$ analogues are effective in treatment of AA. The application of bimatoprost in the treatment of AGA also needs further study. Emer et al. (34) reported a case of female-pattern androgenetic alopecia (AGA) patient who failed to respond to injected 0.03% bimatoprost solution. Numerous clinical trials on using bimatoprost in AGA are currently registered in the US National Institutes of Health Clinical Trials database (https://clinicaltrials.gov) (Table SI[1]) and the results on efficacy and safety of bimatoprost in AGA will be reported on publication of these trial results.

Although latanoprost and bimatoprost are generally safe, patients should be informed about and monitored for local and systemic side-effects. The most common local side-effects are eye pruritus, conjunctival hyperaemia, eye irritation, dry eye symptoms, and erythema and hyperpigmentation of the eyelids (31). The association of uveitis and herpetic simplex viral infection has also been documented. Systemic side-effects include upper respiratory tract infection, headache, abnormal liver function tests, and asthenia. Although no foetal malformations have been reported, bimatoprost is classified as a Food and Drug Administration (FDA) category C medicine because of potential side-effects.

Despite the publication of many clinical reports and studies of PG-induced hair growth, the underlying mechanisms are largely obscure. The effects of bimatoprost treatment are believed to result from longer duration of anagen, increased hair bulb thickness, and increased melanogenesis (35). Mouse studies of latanoprost have suggested that telogen follicles are inducted into the anagen phase within 8 days of treatment (36). In one study using a murine model, mice receiving bimatoprost 0.03% ophthalmological solution once daily for 14 days were compared with mice treated with vehicle control. Every hair follicle of each eyelid was classified into a phase of the hair cycle (37). The bimatoprost-treated group demonstrated a significantly greater proportion of anagen follicles and a decrease in telogen and late catagen follicles, suggesting that bimatoprost extends the duration of the anagen phase.

Studies have also reported other PG analogues with hypertrichosis effects, such as travoprost (38). PGE_2 has been shown to protect mice from radiation-induced alopecia (39). Minoxidil was the first FDA-approved topical medicine for the treatment of AGA. The effect of minoxidil on hair growth is well known. Even though potassium channel opening, leading to increased cutaneous blood flow and stimulation of dermal papilla activity, has been proposed as the mechanism of the effect of minoxidil on hair growth, its exact mechanism of action on hair growth is uncertain (40). Studies have also suggested that minoxidil enhances hair growth by increasing the production of PGE_2 and inhibiting prostacyclin synthesis by cultured dermal papilla cells (40, 41), further confirming the stimulating effects of PGs on hair growth.

PROSTAGLANDIN-INHIBITED HAIR GROWTH

That PGs stimulate hair growth has long been confirmed by evidence. However, the inhibiting effects of PGs on hair growth have not been given attention until recently.

Several COX-2 over-expression transgenic mouse models have been developed with characteristic phenotypes of hair dysregulation. Neufang et al. (42) developed a heterozygous transgenic mouse model using a bovine keratin 5 promoter to direct COX-2 expression in the basal cells of the interfollicular epidermis and the pilosebaceous unit. The constitutive overexpression of COX-2 led to delayed hair follicle morphogenesis, reduced hair follicle density, sebaceous gland hyperplasia, and profound hyperplasia in the scale epidermis of the tail with foci exhibiting signs of dysplasia (42). Bol et al. (43) generated a transgenic mouse model that overexpressed COX-2 under the control of human keratin 14 promoter, which presented with distinct alopecia. Atrophy of the skin, pyknotic nuclei, and enlargement of sebaceous glands were also observed in the K14-COX-2 transgenic mice. Administration of celecoxib (a selective COX-2 inhibitor) restored hair growth, further indicating that the alopecia was due to elevated COX-2 activity. Müller-

Decker et al. (12) described a homozygous transgenic mouse model with COX-2 overexpression under the control of keratin 5 promoter. The overexpression of COX-2 induced a precocious entry into the first catagen stage and a subsequent disturbance of the hair follicle cycle. Alopecia and sebaceous gland hyperplasia were also observed, and inhibition of transgenic COX-2 activity with the specific COX-2 inhibitor suppressed the development of alopecia (12). However, further studies on the COX-2 expression pattern and PGE_2 metabolism did not succeed in clarifying the exact relationship between PGs and inhibition of hair growth.

It was not until PGD_2 was confirmed as inhibiting hair growth in patients with AGA that researchers began to pay attention to the inhibiting effects of PGs in hair growth. Garza et al. first reported the elevation of PTGDS and PGD_2 in the bald scalp compared with the haired scalp of men with AGA (14). During normal follicle cycling in mice, Ptgds and PGD_2 levels increase immediately before the regression phase, suggesting their inhibitory effect on hair growth. Garza et al. further confirmed that PGD_2 inhibited hair growth through DP2 and not through DP1. Using wound-induced hair follicle neogenesis (WIHN) as a marker of skin regeneration, they also confirmed that PGD_2 decreased hair follicle neogenesis (44). Exogenous application of PGD_2 decreased WIHN in wild-type mice and the PGD_2 receptor *DP2* null mice showed increased WIHN compared with strain-matched control mice. Recently, Zheng et al. (45) reported that DP2 antagonists reversed the hair growth inhibition mediated by PGD_2 in a dose-dependent manner by reducing PGD2-triggered apoptosis and maintaining keratinocyte proliferation. They further confirmed that topical application of PGD_2 resulted in accelerated entry into catagen in a mouse model, while DP2 antagonists extended the anagen phase. Flow cytometry analysis verified that PGD_2 decreased $Ki67^+$ cells in the secondary hair germ population. Mantel et al. (46) reported that PGD_2 enhanced testosterone metabolism in human keratinocytes, which initially set up the connection between PGD_2 and testosterone metabolism. The role of testosterone and dihydrotestosterone as drivers of AGA is well established. Based on these results, we can conclude that exploration of the role of PGD_2 in inhibiting hair growth via the DP2 receptor and in pharmacological antagonists of DP2 is a potential approach for hair disorder prevention and treatment (Fig. 1).

CONCLUSION

Different prostanoids may have different or even opposing effects on hair follicles through different signalling pathways. Although research on the role of prostanoids and prostanoid receptors in hair follicles has been carried out, more detailed studies are needed to understand their diverse actions on hair growth and signalling profiles. Recent advances have shown that $PGF_{2\alpha}$ analogues and DP2 antagonists have therapeutic potential for hair loss. However, more research is required to clarify the efficacy, safety, and mechanisms of these prostanoids in treating hair disorders.

ACKNOWLEDGEMENT

Funding sources. This work was supported by the Program for the National Science Grant (code: 81602740).

The authors have no conflicts of interest to declare.

REFERENCES

1. Korbecki J, Baranowska-Bosiacka I, Gutowska I, Chlubek D. Cyclooxygenase pathways. Acta Biochim Pol 2014; 61: 639–649.
2. Hata AN, Breyer RM. Pharmacology and signaling of prostaglandin receptors: multiple roles in inflammation and immune modulation. Pharmacol Ther 2004; 103: 147–166.
3. Johnstone MA. Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. Am J Ophthalmol 1997; 124: 544–547.
4. Quist SR, Wiswedel I, Quist J, Gollnick HP. Kinetic profile of inflammation markers in human skin in vivo following exposure to ultraviolet B indicates synchronic release of cytokines and prostanoids. Acta Derm Venereol 2016; 96: 910–916.
5. Colombe L, Michelet JF, Bernard BA. Prostanoid receptors in anagen human hair follicles. Exp Dermatol 2008; 17: 63–72.
6. Joo M, Sadikot RT. PGD synthase and PGD2 in immune resposne. Mediators Inflamm 2012; 2012: 503128.
7. Paus R, Muller-Rover S, Van Der Veen C, Maurer M, Eichmuller S, Ling G, et al. A comprehensive guide for the recognition and classification of distinct stages of hair follicle morphogenesis. J Invest Dermatol 1999; 113: 523–532.
8. Cotsarelis G. Epithelial stem cells: a folliculocentric view. J Invest Dermatol 2006; 126: 1459–1468.
9. Muller-Rover S, Handjiski B, van der Veen C, Eichmuller S, Foitzik K, McKay IA, et al. A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. J Invest Dermatol 2001; 117: 3–15.
10. Thibaut S, De Becker E, Caisey L, Baras D, Karatas S, Jammayrac O, et al. Human eyelash characterization. Br J Dermatol 2010; 162: 304–310.
11. Nguyen JV. The biology, structure, and function of eyebrow hair. J Drugs Dermatol 2014; 13: s12–16.
12. Muller-Decker K, Leder C, Neumann M, Neufang G, Bayerl C, Schweizer J, et al. Expression of cyclooxygenase isozymes during morphogenesis and cycling of pelage hair follicles in mouse skin: precocious onset of the first catagen phase and alopecia upon cyclooxygenase-2 overexpression. J Invest Dermatol 2003; 121: 661–668.
13. Colombe L, Vindrios A, Michelet JF, Bernard BA. Prostaglandin metabolism in human hair follicle. Exp Dermatol 2007; 16: 762–769.
14. Garza LA, Liu Y, Yang Z, Alagesan B, Lawson JA, Norberg SM, et al. Prostaglandin D2 inhibits hair growth and is elevated in bald scalp of men with androgenetic alopecia. Sci Transl Med 2012; 4: 126ra134.
15. Nesher R, Mimouni M, Elnaddaf H, Nemet A, Kidron D. Characterization of prostaglandin F2alpha receptors in human eyelids. Eur J Ophthalmol 2015; 25: 81–84.
16. Blume-Peytavi U, Lonnfors S, Hillmann K, Garcia Bartels N. A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia. J Am Acad Dermatol 2012; 66: 794–800.
17. Coronel-Perez IM, Rodriguez-Rey EM, Camacho-Martinez

FM. Latanoprost in the treatment of eyelash alopecia in alopecia areata universalis. J Eur Acad Dermatol Venereol 2010; 24: 481–485.
18. Ross EK, Bolduc C, Lui H, Shapiro J. Lack of efficacy of topical latanoprost in the treatment of eyebrow alopecia areata. J Am Acad Dermatol 2005; 53: 1095–1096.
19. Faghihi G, Andalib F, Asilian A. The efficacy of latanoprost in the treatment of alopecia areata of eyelashes and eyebrows. Eur J Dermatol 2009; 19: 586–587.
20. Wester ST, Lee WW, Shi W. Eyelash growth from application of bimatoprost in gel suspension to the base of the eyelashes. Ophthalmology 2010; 117: 1024–1031.
21. Yoelin S, Walt JG, Earl M. Safety, effectiveness, and subjective experience with topical bimatoprost 0.03% for eyelash growth. Dermatol Surg 2010; 36: 638–649.
22. Woodward JA, Haggerty CJ, Stinnett SS, Williams ZY. Bimatoprost 0.03% gel for cosmetic eyelash growth and enhancement. J Cosmet Dermatol 2010; 9: 96–102.
23. Smith S, Fagien S, Whitcup SM, Ledon F, Somogyi C, Weng E, et al. Eyelash growth in subjects treated with bimatoprost: a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. J Am Acad Dermatol 2012; 66: 801–806.
24. Kwon O, Kim JY, Paik SH, Jeon HC, Jung YJ, Lee Y, et al. Long-term utility and durability of the therapeutic effects of bimatoprost 0.03% for eyelash augmentation in healthy Asian subjects. Dermatology 2014; 229: 222–229.
25. Yoelin SG, Fagien S, Cox SE, Davis PG, Campo A, Caulkins CA, et al. A retrospective review and observational study of outcomes and safety of bimatoprost ophthalmic solution 0.03% for treating eyelash hypotrichosis. Dermatol Surg 2014; 40: 1118–1124.
26. Fagien S, Walt JG, Carruthers J, Cox SE, Wirta D, Weng E, et al. Patient-reported outcomes of bimatoprost for eyelash growth: results from a randomized, double-masked, vehicle-controlled, parallel-group study. Aesthet Surg J 2013; 33: 789–798.
27. Suwanchatchai W, Tanglertsampan C, Pengsalae N, Makornwattana M. Efficacy and safety of bimatoprost 0.03% versus minoxidil 3% in enhancement of eyebrows: a randomized, double-blind, split-face comparative study. J Dermatol 2012; 39: 865–866.
28. Glaser DA, Hossain P, Perkins W, Griffiths T, Ahluwalia G, Weng E, et al. Long-term safety and efficacy of bimatoprost solution 0.03% application to the eyelid margin for the treatment of idiopathic and chemotherapy-induced eyelash hypotrichosis: a randomized controlled trial. Br J Dermatol 2015; 172: 1384–1394.
29. Zaheri S, Hughes B. Successful use of bimatoprost in the treatment of alopecia of the eyelashes. Clin Exp Dermatol 2010; 35: e161–162.
30. Vila TO, Camacho Martinez FM. Bimatoprost in the treatment of eyelash universalis alopecia areata. Int J Trichology 2010; 2: 86–88.
31. Law SK. Bimatoprost in the treatment of eyelash hypotrichosis. Clin Ophthalmol 2010; 4: 349–358.
32. Roseborough I, Lee H, Chwalek J, Stamper RL, Price VH. Lack of efficacy of topical latanoprost and bimatoprost ophthalmic solutions in promoting eyelash growth in patients with alopecia areata. J Am Acad Dermatol 2009; 60: 705–706.
33. Borchert M, Bruce S, Wirta D, Yoelin SG, Lee S, Mao C, et al. An evaluation of the safety and efficacy of bimatoprost for eyelash growth in pediatric subjects. Clin Ophthalmol 2016; 10: 419–429.
34. Emer JJ, Stevenson ML, Markowitz O. Novel treatment of female-pattern androgenetic alopecia with injected bimatoprost 0.03% solution. J Drugs Dermatol 2011; 10: 795–798.
35. Fagien S. Management of hypotrichosis of the eyelashes: focus on bimatoprost. Plast Surg Nurs 2015; 35: 82–91.
36. Sasaki S, Hozumi Y, Kondo S. Influence of prostaglandin F2alpha and its analogues on hair regrowth and follicular melanogenesis in a murine model. Exp Dermatol 2005; 14: 323–328.
37. Tauchi M, Fuchs TA, Kellenberger AJ, Woodward DF, Paus R, Lutjen-Drecoll E. Characterization of an in vivo model for the study of eyelash biology and trichomegaly: mouse eyelash morphology, development, growth cycle, and anagen prolongation by bimatoprost. Br J Dermatol 2010; 162: 1186–1197.
38. Ortiz–Perez S, Olver JM. Hypertrichosis of the upper cheek area associated with travoprost treatment of glaucoma. Ophthal Plast Reconstr Surg 2010; 26: 376–377.
39. Hanson WR, Pelka AE, Nelson AK, Malkinson FD. Subcutaneous or topical administration of 16,16 dimethyl prostaglandin E2 protects from radiation-induced alopecia in mice. Int J Radiat Oncol Biol Phys 1992; 23: 333–337.
40. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. Br J Dermatol 2004; 150: 186–194.
41. Michelet JF, Commo S, Billoni N, Mahe YF, Bernard BA. Activation of cytoprotective prostaglandin synthase-1 by minoxidil as a possible explanation for its hair growth-stimulating effect. J Invest Dermatol 1997; 108: 205–209.
42. Neufang G, Furstenberger G, Heidt M, Marks F, Muller-Decker K. Abnormal differentiation of epidermis in transgenic mice constitutively expressing cyclooxygenase-2 in skin. Proc Natl Acad Sci U S A 2001; 98: 7629–7634.
43. Bol DK, Rowley RB, Ho CP, Pilz B, Dell J, Swerdel M, et al. Cyclooxygenase-2 overexpression in the skin of transgenic mice results in suppression of tumor development. Cancer Res 2002; 62: 2516–2521.
44. Nelson AM, Loy DE, Lawson JA, Katseff AS, Fitzgerald GA, Garza LA. Prostaglandin D2 nhibits wound-induced hair follicle neogenesis through the receptor, Gpr44. J Invest Dermatol 2013; 133: 881–889.
45. Zheng Y HJ, Rosengard H, Nace A, Ma G, Geyfman M, Lichtsteiner S, Washenik K, Cotsarelis G. Effect of prostaglandin D2 on hair follicle growth and its impact on hair follicle tem/progenitor cells. J Invest Dermatol 2016; 2016. p. 124.
46. Mantel A MT, Goldsborough K et al. Prostaglandin D2-enhanced testosterone metabolism in human keratinocytes is mediated by reactive oxygen species. J Invest Dermatol 2016; 136: 123.
47. Elias MJ, Weiss J, Weiss E. Bimatoprost ophthalmic solution 0.03% for eyebrow growth. Dermatol Surg 2011; 37: 1057–1059.
48. Schweiger ES, Pinchover L, Bernstein RM. Topical bimatoprost for the treatment of eyebrow hypotrichosis. J Drugs Dermatol 2012; 11: 106–108.
49. Beer KR, Julius H, Dunn M, Wilson F. Treatment of eyebrow hypotrichosis using bimatoprost: a randomized, double-blind, vehicle-controlled pilot study. Dermatol Surg 2013; 39: 1079–1087.
50. Vergilis-Kalner IJ. Application of bimatoprost ophthalmic solution 0.03% for the treatment of eyebrow hypotrichosis: series of ten cases. Dermatol Online J 2014; 20.
51. Harii K, Arase S, Tsuboi R, Weng E, Daniels S, VanDenburgh A. Bimatoprost for eyelash growth in Japanese subjects: two multicenter controlled studies. Aesthetic Plast Surg 2014; 38: 451–460.
52. Ochoa BE, Sah D, Wang G, Stamper R, Price VH. Instilled bimatoprost ophthalmic solution in patients with eyelash alopecia areata. J Am Acad Dermatol 2009; 61: 530–532.
53. Zaher H, Gawdat HI, Hegazy RA, Hassan M. Bimatoprost versus mometasone furoate in the treatment of scalp alopecia areata: a pilot study. Dermatology 2015; 230: 308–313.
54. Li AW, Antaya RJ. Successful treatment of pediatric alopecia areata of the scalp using topical bimatoprost. Pediatr Dermatol 2016; 33: e282–283.