Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (9) Issue (11) (2024), (53 - 58) **online: ISSN 2356–976x**
http://bjas.bu.edu.eg
Medical and Health Science

Alpha Smooth Muscle Actin role in Androgenetic Alopecia Pathogenesis

Yasmin A.Ibrahim[1], Ghada M.Abdel Khalik[1], Rehab M.Salem[1]and Rasha M.Abdrabbou[2]
[1]Dermatology, Venerology and Andrology Dept., Faculty of Medicine, Benha University, Benha, Egypt
[2] Clinical and Chemical Pathology Dept., Faculty of Medicine, Benha University, Benha, Egypt
E-Mail: Yasminahmed4488@gmail.com

Abstract
Background: Up to 80% of men and 50% of women will have androgenetic alopecia (AGA) at some point in their lives, making it the most prevalent kind of hair loss. As a result of the actions of dehydrotestosterone (DHT), a testosterone metabolite, on androgen-sensitive hair follicles, the width, length, and color of affected hair gradually decrease in AGA. The arrector pili muscle is made up of fusiform cells that don't have cytoplasmic striations and have centralized, cigar-shaped nuclei. These muscles round the hair follicle in the bulge area and are linked to it at an acute angle. Research has shown that the dermal sheath of hair follicles in both rats and humans contains alpha smooth muscle-actin (α-SMA), however this protein is not found in the dermal papilla cells. In this post, we will take a look at the pathophysiology of androgenic alopecia and how Alpha Smooth Muscle Actinin plays a part in it. The loss of structural integrity in hair follicles might be one way that α-SMA contributes to AGA. In the vertex area of AGA patients, the expression of α-SMA is significantly reduced. In addition, compared to the occipital area, the vertex region of AGA patients shows considerably decreased α-SMA expression.

Keywords: Hair follicle, androgenetic alopecia (AGA), as well as alpha smooth muscle-actin (α-SMA).

Introduction

Hair thins out, becomes shorter, and loses color as a result of AGA. Dehydrotestosterone (DHT), a byproduct of testosterone, triggers hair loss in androgen-sensitive hair follicles. Diffuse thinning of the crown area and preservation of the frontal hairline characterize the Ludwig pattern of alopecia are symptoms experienced by women with AGA. In male pattern baldness, the frontal hairline recedes somewhat behind the ear and then thins out diffusely at the vertex [1].

It was formerly thought that each hair follicle was connected to its own APM.Histological sections reveal concentrated nuclei that are "cigar shaped" and characterized by the fusiform shape of the arrector pili (APM) cells. The cytoplasm of these cells is devoid of striations. Typically, the APM appears as a metachromatic structure on the follicle's side that forms an acute angle with the skin's surface. On both terminal and vellus hairs, the APM's proximal end encircles the whole follicle in the bulge area [2].

Human follicles, rat pelage, and rat vibrissa all included smooth muscle alpha-actin in their dermal sheath components. The antigen was not expressed by dermal papilla cells in any of the follicle types. Nevertheless, this antibody stained a significant portion of the dermal papilla and dermal sheath cells in cultured hair. When examined with a desmin antibody, the same cells came back negative [3].

Materials and methods

Data Sources: A literature review was conducted using the Medline databases (Pub Med and Medscape) to gather information on the causes, etiology, and decrease of androgenic alopecia (AGA), as well as the involvement of Alpha Smooth Muscle Actinin. The review will cover the years up to 2024.

Choosing the Right Study: Independent reviewers choose which papers to include. Inclusion was contingent upon them meeting the following requirements: 1. Expressed and made public in English. 2. Featured in respected journals that undergo a rigorous peer review process. 3. Examine the origins and pathophysiology of AGA, and talk about how Alpha Smooth Muscle Actinin contributes to the disease.

Data Extraction: Research was deemed ineligible if it failed to meet the specified requirements. Ethical permission, clear eligibility criteria, suitable controls, sufficient information, and well-defined evaluation measures were all variables in determining the study's quality. We used a data collecting form to independently extract information relevant to our research results from all qualifying studies.

Literature review:

Hair loss caused by androgens (AGA) The progressive reduction, ineffectiveness, or death of hair follicles characterises androgenetic alopecia (AGA), sometimes called pattern alopecia, a kind of non-scarring hair loss. It affects more men than women and is the most prevalent kind of hair loss [4]. It is known as female AGA (FAGA) when it happens in females and male AGA (MAGA) when it happens in men. There is a distinction between

AGAs that begin before age 30 and those that begin after age 50 [5].

AGA is mostly influenced by heredity and the androgen hormone. But oxidative stress and persistent micro inflammation are only two of many additional potential contributors. Some research has connected AGA to metabolic syndrome, prostate cancer, coronary heart disease, and inducing chronic inflammation. Anxiety, despair, and a generally worse quality of life are more common symptoms of AGA compared to alopecia areata, which lessens the emotional toll [6].

The Causes and Effects of AGA Hair gradually thins down as a consequence of androgenetic alopecia, which is defined by a decrease in the ratio of long vellus hairs to short terminal hairs. Follicular shrinkage of hair occurs only in certain parts of the scalp; in males, it's the frontotemporal and vertex areas, while in women, it's the crown region. Androgens have the potential to cause harm in certain parts of the scalp. Miniaturization of hair follicles is the only change in AGA. The gradual receding of hairline and, in rare occasions, a rise in hair loss occur many years before the visible signs of baldness. This is because not all follicles undergo follicular shrinkage at the same time during AGA [7]. It is believed that a reduction in the number of cells per papilla causes the dermal papilla volume to diminish, leading to follicular shrinkage [8].

What Causes AGA? Genetic and environmental factors interact to produce AGA, a complex condition. A hallmark of this condition is hair thinning, which occurs when terminal hair follicles undergo a transformation into vellus hairs as a result of changed dynamics in the hair cycle [9].

An androgen-dependent disorder, AGA affects only those who are genetically susceptible to it. While a lesser genetic tendency may allow hair loss to occur in one's 60s or 70s, a stronger one might cause baldness to begin at an earlier age. Men acquire the baldness gene from their fathers' side, whereas women receive it from their mothers' side [10].On the X-chromosome, you'll find the androgen receptor (AR) gene, which is passed down from mom. For early-onset AGA, AR gene variability is significant [6].

Elements of Hormones

The process of hair follicle shrinkage relies heavily on androgens. The dermal papilla is the principal androgen target in hair follicles, as AR is concentrated there rather than in the outer root sheath or bulge [11]. Although the exact function of androgens in female AGA is not well understood, it is widely believed that AGA in both sexes originates from aberrant sensitivity of scalp hair follicles to circulating androgens [12].

The state of inflammation

Mild perifollicular lymphohistiocytic infiltration is seen in about 40% of AGA cases. This infiltration is occasionally accompanied by concentric layers of perifollicular collagen deposition and, on rare occasions, eosinophils and mast cells. Follicle stelae and lower follicles are sometimes impacted by cellular inflammatory alterations as well [13].

Distinct Elements

a. Environmental variables: When AGA first appears or becomes worse, environmental variables may play a role. Environmental contaminants, such as endocrine-disrupting chemicals (EDCs), may cause AGA to begin early in life[14]. Smoking and exposure to UV radiation are other suspected contributors to AGA development.
b. Thyroid Abnormalities: Hair loss may be a symptom of hypothyroidism or another parathyroid disease; in rare cases, generalized hair loss can be an early indicator of the condition. The development and maintenance of healthy hair follicles depend on thyroid hormone. In women who have severe hypothyroidism, the complex interplay between thyroid hormones and androgens may have a role in AGA [15].
c. Inadequate Vitamin D Levels: The treatment of hair loss is influenced by the levels of vitamin D in the blood. Keratinocyte stem cells in the bulge region of the hair follicle rely on the vitamin D3 receptor. A lack of vitamin D may interfere with the hair follicle cycle and hinder the regeneration of stem cells. Patients presenting with hair loss should have their blood vitamin D3 levels checked in addition to other hormone tests because of the correlation between low serum vitamin D3 levels and an increased risk of female pattern hair loss (FPHL).[16].

Indicators of Androgenetic Alopecia in Clinical Practice

- Hair thinning in men

According to the Hamilton-Norwood scale, AGA mostly affects the vertex and frontotemporal region in males. Though it more often affects women, males may sometimes suffer from extensive crown thinning and frontal hairline retention in a pattern comparable to the Ludwig type [17].

There is a distinct pattern to the hair loss that starts above the temples and moves

downwards. Over time, the hairline thins down and becomes the signature "M" shape. In addition, thinning hair on top might cause bald spots or even complete thinning. A deeper bitemporal recession, measuring about an inch, is a hallmark of MPHL. This recession continues beyond the frontal hair line. This disorder may have a therapeutic response if caught early enough [18].

- Loss of hair in a pattern

Hair loss in women: In female AGA, the condition is characterized by a gradual receding of the hairline and a broadening of the crown region, whereas the frontal hair line remains intact. A 'Christmas tree' pattern describes the typical symptom progression. The patient's hairline (85%) and temples region (90%) are the areas most often found to be retained throughout the examination [19].

- AGA of early onset

There isn't a universally accepted definition of early-onset AGA, although it's usually thought of as AGA that manifests before the age of 30 or 35. Although AGA is more common in older adults, there is a significant proportion of cases that manifest early in life, with prevalence rates ranging from 19.2% to 57.6% in various groups [20].

- Adolescent AGA

Puberty and adrenarche have begun at earlier ages in the last hundred years, perhaps as a result of hyperinsulinemic diets and increasing exposure to environmental hormones and sexuality. Therefore, it is hypothesized that the higher rates of circulating androgens in this group cause genetically predisposed children to acquire AGA at an earlier age, contributing to the higher frequency of pediatric AGA. [21]. Özcan demonstrated that AGA does not cause prepubertal adolescents to have androgenic hormone levels in their blood that are higher than what is typically seen at this stage of sexual development. This finding lends credence to the idea that adrenal androgens have a direct role in AGA in children, rather than gonadal androgens [22]. Similar to the adult male pattern of hair loss, most males experience thinning hair in the vertex and bitemporal areas throughout adolescence. But among teenage males with AGA, a feminine pattern may be seen [21].

Actins, which are proteins found in eukaryotic organisms, have a role in several cellular processes such as muscle contraction, cell movement, cell attachment, cell proliferation, and cell shape regulation. There are six related proteins in vertebrates' actin family, and their expression patterns vary greatly during development and across tissues. These six functional actin genes are distributed across many chromosomes [23].

Vascular smooth muscle actin, an isoform, is encoded by the ACTA2 gene. Smooth muscle cells lining blood vessels are mainly responsible for contracting and facilitating vascular movement. Wound, scar, and fibrocontractive lesion healing involves myofibroblasts, a non-muscle cell type. Thin filaments made of α-SMA and thick filaments made of SMC-specific β-myosin interact to determine the contractile function of α-SMA [24].

How α-SMA Is Structured Molecularly

Within eukaryotic cells, four unique actin variants exist: two that are restricted to vascular SMCs (α-SM and γ-SM) and two that are located in the cytoplasm (β-NM and γ-NM). The contractile capabilities of α-SMA, which impact arterial tones and myofibroblast activation, are mainly regulated by its location in the microfilament bundles of vascular smooth muscle cells (SMCs). From birds to humans, the main structure of each of the six actin isoforms remains constant [25].

What α-SMA Does

Studying the role of α-SMA at its N-terminus demonstrates that actin isoforms vary primarily in their N-terminal sequence, indicating that unique binding mediates their specialized roles. The monoclonal antibody anti-α-SM-1 recognizes the Ac-EEED, which is the N-terminal sequence of α-SMA. Laboratory tests demonstrate that the anti-α-SM-1 and its Fab component promote the polymerization of α-SMA [26].

1. Wound healing

α- During wound contraction, SMA is abundant in granulation tissue; however, when myofibroblasts die off and scar tissue forms, SMA is no longer present. It seems that hypertrophic scar development might be due to myofibroblast not undergoing apoptosis at the right moment throughout the healing process. Evidence suggests that fully differentiated myofibroblasts remain in cardiac granulation tissue for an extended period after an infarct. In such a case, angiotensin II may be crucial in the development of fibrosis. It is likely that the constant stress in these locations is the reason why fibroblastic cells express α-SMA in old cardiac scars [27].

26. Cells of tumors The temporary expression of α-CAA and α-SMA during skeletal muscle development, as well as the marker status of α-SKA, have been well shown. Therefore, several RMS have an actin isoform expression pattern that is similar to the stages of skeletal muscle development: α-SKA expression in the embryonal subtype indicates a greater degree

of differentiation in these tumors, whereas RMSs positive for just α-CAA and α-SMA indicate an early developmental stage. Immunohistochemical screening using actin isoform-specific antibodies, in conjunction with the already recognized tumor markers, could make RMS detection easier, according to these data [28].

27, Reaction involving chromosomes "Wounds that do not heal" is one way to characterize epithelial tumors. Like wound healing or fibrosis, tumor cells stimulate neighboring stromal tissues via the production of growth factors. The secretion of matrix metalloproteinases (MMPs) and cytokines, such as TGF-β, FGF-2, and PDGF, by activated fibroblasts and macrophages triggers angiogenesis, induces fibroblast differentiation into myofibroblasts, and potentiates tumor development [29].

Breast, liver, lung, colon, stomach, prostate, and pancreatic invasive and metastatic carcinomas often exhibit activated cells with myofibroblastic characteristics as indicators of stromal responses. It is worth noting that myofibroblasts often manifest before cancer reaches its invasive stage, which underscores their significance in the change from a non-invasive to an aggressive phenotype [30].

28. Heart disease Atheromatous plaque and restenosis after percutaneous angioplasty develop and progress via the processes of smooth muscle cell reproduction and migration into the inner layer of the vessel. The proportion of actin isoforms differs in different types of smooth muscles; visceral smooth muscles mostly contain γ-smooth muscle actin (γ-SMA), whereas vascular smooth muscles primarily include α-smooth muscle actin (α-SMA) [31].

It is also possible for cells originating from bone marrow to develop into SMCs in atherosclerotic lesions. In vitro experiments have shown that stem cells found in the adventitia may develop into cells that exhibit SMC markers such α-SMA, SM22, calponin, and SM-MHC. Future research should focus on determining whether or not these animal model findings are applicable to the development of atherosclerosis in humans [32].

29. Heart muscle Two main types of sarcomeric actin, α-skeletal actin (α-SKA) and α-cardiac actin (α-CAA), are found in healthy adult myocardium. Their transcript levels change according on the species, stage of development, and disease. The beginning of cardiomyocyte differentiation is signaled by α-Smooth muscle actin (α-SMA), which is subsequently replaced by α-SKA and α-CAA as the cell matures. These genes are indicators of cardiac hypertrophy because they are re-expressed throughout the process, and this shift may be essential for varying degrees of myocardial contractility [31].

In vivo throughout development, varying degrees of cardiac contractility are achieved by the successive production of muscle actin isoforms. In vitro, in cultivated cardiomyocytes, both adult and newborn cells re-express proteins indicative of fetal development. Included in this category are α-SMA, α-SKA, β-myosin heavy chain (β-MHC), and atrial natriuretic factor (ANF). Furthermore, these genes are indicators of heart hypertrophy in vivo because they are re-expressed throughout the process [33].

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