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Application of multi-omics techniques to androgenetic alopecia: Current status and perspectives

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ABSTRACT

The rapid advancement of sequencing technologies has enabled the generation of vast datasets, allowing for the in-depth analysis of sequencing data. This analysis has facilitated the validation of novel pathogenesis hypotheses for understanding and treating diseases through *ex vivo* and in vivo experiments. Androgenetic alopecia (AGA), a common hair loss disorder, has been a key focus of investigators attempting to uncover its underlying mechanisms. Abnormal changes in mRNA, proteins, and metabolites have been identified in individuals with AGA, and future developments in sequencing technologies may reveal new biomarkers for AGA. By integrating multiple omics analysis datasets such as genomics, transcriptomics, proteomics, and metabolomics—along with clinical phenotype data—we can achieve a comprehensive understanding of the molecular underpinnings of AGA. This review summarizes the data-mining studies conducted on various omics analysis datasets as related to AGA that have been adopted to interpret the biological data obtained from different omics layers. We herein discuss the challenges of integrative omics analyses, and suggest that collaborative multi-omics studies can enhance the understanding of the complete pathomechanism(s) of AGA by focusing on the interaction networks comprising DNA, RNA, proteins, and metabolites.

1. Introduction

Androgenetic alopecia (AGA), which is a prevalent form of hair loss affecting both men and women, is characterized by a genetic predisposition and heightened sensitivity to androgens. In male pattern hair loss (MPHL), hair loss typically initiates at the temples, resulting in a receding hairline or thinning at the crown [1]. Conversely, female pattern hair loss (FPHL) occurs between the vertex and the front of the scalp without impacting the hairline. The pathological mechanism of AGA involves disruptions in the hair growth cycle, leading to a shortened growth phase and premature cessation of catagen and telogen. Additionally, there is a gradual reduction in the diameter of the hair follicle and the hair shaft as new hair grows, ultimately causing the miniaturization of the hair follicle [2,3]. Furthermore, an increasing number of studies have indicated a potential association between AGA and other significant pathological conditions, including coronary artery disease, hyperinsulinemia, polycystic ovarian syndrome, hypertension, and prostate cancer. This suggests the existence of a common underlying biological basis [4–7]. To gain deeper insights into the pathogenesis of AGA and explore potential treatment options, researchers have increasingly turned to multi-omics technologies. This interdisciplinary field encompasses various technologies such as genomics, transcriptomics, proteomics, and metabolomics [8], offering valuable insights into both basic and clinical medicine. Numerous studies have identified variations in mRNA, proteins, and metabolites in AGA patients, enriching our understanding of the pathogenesis of AGA [9]. Through the integration of multi-omics technologies, researchers can acquire a holistic understanding of the pathogenesis of AGA, pinpoint novel therapeutic targets, and customize personalized treatment strategies. This review presents a comprehensive overview of recent omics research on AGA and future challenges in the field.

2. Development of AGA

AGA, also known as premature baldness, is a common cause of progressive hair loss affecting both men and women. It typically starts

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during or after puberty and is characterized by hair thinning[10]. It has a long-lasting impact on an individual's quality of life, as well as their physical and mental well-being. The primary clinical sign of the condition is the shortening of the anagen phase of the hair follicle, leading to the miniaturization of the follicle and the replacement of fine, lightly pigmented hairs with coarse, pigmented, medullated terminal hairs[11]. The primary factor contributing to AGA is the conversion of testosterone (T) to dihydrotestosterone (DHT) in the scalp by 5α-reductase, which subsequently increases binding to the androgen receptor (AR). However, there is no evidence that serum androgen levels are associated with AGA [12,13].

Researchers employ various methods to investigate AGA, including genetic studies to identify susceptibility genes[14,15], hormonal assays to measure androgen levels[12], histologic analysis of scalp biopsies to observe follicular changes[11], and in vitro studies using cell culture models to explore the effects of androgens on hair follicle function. Moreover, clinical trials have been conducted to assess the effectiveness of treatments such as topical minoxidil and oral finasteride in managing AGA[16,17]. Despite these efforts, there are limited clinically proven treatments for AGA, making it a contentious and complex issue to explore therapeutic targets beyond androgens, their receptors, and type II 5α-reductase in the development of AGA.

3. Multi-omics approaches

Current treatments for AGA include FDA-approved oral and topical medications such as finasteride and minoxidil. The conventional drug-discovery process is time-consuming and may result in uncertainties and side-effects; therefore, to overcome these challenges, various alternative therapies are currently under intensive investigation. These include gene editing through CRISPR/Cas9 technology or RNAi, the utilization of growth factors such as epidermal growth factor and platelet-derived growth factor to encourage the proliferation and differentiation of hair follicle cells, platelet-rich plasma for follicle repair, and low-energy laser therapy (LLLT) and photodynamic therapy to stimulate hair growth. Additionally, personalized treatment of AGA can be achieved through the application of multi-omics techniques. Omics methods have thus become essential tools in biomedical research, allowing for a deeper insight into genetic, protein, and metabolite changes in diseases at the tissue or cellular level.

3.1. Genomics

Genomics, the study of an organism's complete genome, has advanced from analyzing single genes to thousands, providing insights into the complete genetic makeup of an organism [18]. The genomics field has expanded to investigate expression profiles and protein functions, complementing other omics methodologies. Essential techniques such as gene sequencing provide detailed information on the complete sequence of a genome, uncovering structural details, mutations, and genetic variations. Other genomics tools include genome assembly, gene annotation, expression profiling, functional genomics, and variant analysis[19]. Genomics research of AGA utilizes genome-wide association studies (GWAS) and next-generation sequencing (NGS) to identify differentially expressed genes.

3.2. Transcriptomics

Transcriptomics, a field developed after genomics, focuses on studying the RNA present in a tissue or cell under specific conditions, providing insights into the properties of the genome in various physiologic or pathologic states. The primary goal is to investigate the quantity and types of RNA in tissues or cells under specific functional conditions [20,21]. Research in this field is typically categorized into two main methods: hybridization-based techniques that principally apply microarray technology [22], and sequencing-based approaches such as RNA sequencing, which is commonly employed in autoimmune disease research [23]. Apart from detailing an RNA sequence, transcriptomic technologies also reveal information on gene expression, novel transcriptional events, isoform variations, nucleic acid polymorphisms, allele-specific expression, and more. Essential techniques in transcriptomic studies include miRNA sequencing, single-cell transcriptomics, spatial transcriptomics, and analysis of transcription-factor binding sites.

3.3. Proteomics

Proteomics is the comprehensive study of all proteins within a biological system or sample and exploits gel electrophoresis and mass spectrometry for the analysis of protein composition, expression, and modifications. It can quantitatively and qualitatively describe all proteins present in cells, tissues, or organisms, with the primary objective to gain insights into protein interactions, functions, and cellular activities. Key tools in proteomics research include protein microarrays and functional-enrichment analysis [24].

3.4. Metabolomics

Metabolomics is a valuable tool for investigating small-molecule metabolites within metabolic pathways. This approach involves both qualitative and quantitative analysis of metabolites over time and explores their diversity and abundance under varying conditions, providing a comprehensive understanding of an organism's functional level and drug-action mechanisms [25,26]; it is often used for biomarker discovery [27]. Common techniques in metabolomics include gas chromatography and liquid chromatography, and is often followed by statistical analysis once samples are identified using nuclear magnetic resonance. These methods facilitate the precise and sensitive identification of potential disease biomarkers.

4. Application of omics technologies to the study of AGA

Various combinatorial methods have been explored and applied to the study of AGA. Table 1 provides an overview of the approaches adopted in omics research, including genomics, transcriptomics, proteomics, and metabolomics.

4.1. Genomic technologies in AGA

We summarize in Table 2 the differentially expressed transcripts (DETs) or differentially expressed genes (DEGs) in AGA as obtained by genomic analysis.

4.1.1. DNA sequence variation

Midorikawa et al. conducted a study using DNA microarray to analyze gene-expression profiles in dermal papilla cells (DPCs) from patients with AGA. These authors identified 107 DEGs in DPCs: of these DEGs, 38 genes were upregulated, including the cell-cycle checkpoint gene cyclin-dependent kinase inhibitor p16. Conversely, 69 genes were downregulated, including the cell-cycle regulatory genes cyclin B and cyclin D1, as well as various signal transduction and growth factor genes. Previous research has indicated that the downregulation of BMP2 [31–33] and ephrinA3 is implicated in the regulation of the hair cycle [9]. Benjamin et al. analyzed single-cell chromatin profiles and transcripts from scalp tissues of both healthy individuals and patients with alopecia areata, identifying diverse cell types within hair follicle niches. Their study revealed a greater number of enhancer-gene links compared to previous investigations, utilizing gene-regulation maps to prioritize cell types, genes, and causal variants related to AGA, eczema, and other complex traits. GWAS signals for AGA were notably enriched in the regulatory regions of DPCs, highlighting their significance in AGA pathogenesis. Moreover, their study predicted potential functional

Table 1
Selected methodologies used in omics in AGA.

Identification	Omics methodology	Other approaches	Species/ sample	Main Finding	References
107 differentially expressed genes (DEGs)	DNA microarray		Human/ dermal papilla cells (DPCs)	Numerous cell cycle-related proteins are implicated in differentially expressed genes	Midorikawa et al.
Diverse cell types within hair follicle niches	Single-cell chromatin profiles/ transcripts		Human/ scalp tissues	Revealed a greater number of enhancer-gene links compared to previous investigations	Benjamin et al.
The contribution of rare genetic variants to the development of MPHL	Exome sequencing		Human	Five significant genetic associations	Sabrina et al.
Impact of AR gene polymorphism on the effectiveness of finasteride treatment in addressing AGA	Gene polymorphism		Human	Making use of the quantity of GGC sequences as a possible AGA predictor	Ghassemi et al.
3D co-cultured DPCs offer a more accurate representation	Global transcriptome analysis	2D and 3D co-culture technique for cells	Human	AGA may be associated with chemokines and IL-17 pathways, which offer the first global transcriptome of DPCs in 2D and 3D co-cultured models treated with DHT	Zhang et al.
Down-regulation of three ion channel markers (*LRRC26*, *KCNK5*, and *B3GNT3*) in AGA	RNA microarray analysis		Human	Significant upregulation of key inflammatory regulators	Miao et al.
JAG1 gene as a susceptibility locus for AGA in males	RNA microarray analysis		Human	Notch signalling pathway as a major disrupted pathway in AGA	Karnik et al.
Slightly elevated levels of inflammatory markers were found in AGA-affected scalp skin and subcutaneous tissue	RNA microarray analysis	Non-invasive sample collection methods	Human/ hair follicles (HF)	Differential expression of genes related to RNA methylation, ion channel regulation, hair keratin synthesis, and hair cycle regulation	Vogt et al.
Increase in the levels of the Wnt pathway inhibitor pigment epithelium-derived factor (*PEDF*) and secreted frizz-related protein 1 (*SFRP1*)	RNA microarray analysis		Human/ HF	Providing further evidence for the role of Wnt inhibition in AGA	Philpott et al.
WNT10A may play a functional role in the pathogenesis of AGA	Differential gene ontology enrichment analysis		Human	WNT signaling, apoptosis, cell proliferation, and disordered neural pathways are crucial elements in the alopecia process	Dey et al.
32 DEGs	RNA sequencing	ReactomeFIViz application	Human	WNT and TGF signaling were linked to down-regulated DEGs, whereas pathways related to oxidative stress were linked to up-regulated DEGs	Premanand et al.
Identified target genes of the Wnt/ β-catenin pathway	RNA sequencing	Immunofluorescence staining Microarray RT-PCR Western blotting	Human	Inhibitors (*AXIN2, DKK-1*) and activators (*LEF1, FZD7*) of the WNT pathway are up-regulated after Wnt3a treatment	Shin et al.
Up-regulated genes were predominantly involved in lipid synthesis and electron carrier activity/transport	RNA sequencing		Human/ HF/ DPCs	Reduced DPC levels in balding scalps may prevent blood vessels from forming around hair follicles	Chew et al.
410 upregulated transcripts and 318 downregulated transcripts	RNA sequencing Gene clustering		Human/ HF	650 nm red light stimulation may enhance hair follicle growth by influencing biological processes like leukocyte transendothelial migration, metabolism, and adhesion	Yang et al.
511 differentially expressed genes identified in AGA patients compared to healthy individuals	RNA sequencing		Human/ Scalp tissue	Differentially expressed genes are primarily associated with human infectious diseases and microenvironmental signalling pathways	Qu et al.
ATF3 and *NAPA* may suppress oxidative stress-related pathways in AGA progression	Single-cell sequencing		Human	Link abnormal hairiness in AGA to oxidative stress	Ku et al.
Heterogeneity of DPCs during hair follicle development	Single-cell sequencing	In vitro culture of hair follicles	Human/ HF	Accurately describing the gene expression profiles of hair stem cells and inner hair root sheath (IRS)	Ge et al.
Comparison of transcriptome profiles between normal and miniaturized hair follicles in AGA	Transcriptomics (Non-coding RNA)		Human/ HF	Hormone receptors, particularly those in the PPAR pathway, played a role in follicle miniaturization	Bryan et al.
506 mRNAs and 55 microRNAs that were differentially expressed in AGA vertex HF	Transcriptomics (Non-coding RNA)		Human/ HF	Abnormal expression of miR-133b potentially leading to inactivation of the Wnt/β-catenin pathway	Liu et al.
Signaling molecules and miRNA expression profiles	Transcriptomics (Non-coding RNA) Proteomics	Two-dimensional electrophoresis separation Mass spectrometry identification Protein database retrieval	Mouse	Differential expression of non-coding RNAs at different times of the hair follicle cycle	Xu et al.

(*continued on next page*)

Table 1 (*continued*)

Identification	Omics methodology	Other approaches	Species/ sample	Main Finding	References
Pioneering study on lncRNAs associated with AGA	Transcriptomics (Non-coding RNA)		Human	Alterations in lncRNAs and their target genes that could potentially serve as new targets for the prevention and treatment of AGA	Bao et al.
Gene expression in patients with moderate and severe AGA	High-throughput sequencing			There are 421 downregulated and 284 upregulated genes in the hair loss and non-hair loss domains	Liang et al.
Molecular mechanisms underlying DPC aggregation	Proteomics		Human/ DPCs	Mitochondrial ribosomal protein S7 (MRPS7) and heat shock protein 70 (HSP70) as factors in the aggregation behavior of cultured DPCs	Xia et al.
Differential expression of hair follicle cycle-related proteins	Proteomics		Human/ DPCs	These proteins play roles in Ca2 + -regulated biological processes, migration, and signal regulation	Wang et al.
28 types of DPC-specific extracellular matrix proteins	Shotgun proteomics	Network analysis	Human/ DPCs	ITGB1, IGFBP3, and THBS1 were selected as potential biomarkers of hair growth-regulating proteins	Won et al.
Different protein expression patterns at various stages of the hair growth cycle	Proteomics	Bioinformatic Cluster analysis	Human/ DPCs	Annexin A1, Vimentin and Lamin A/C are dynamically up-regulated in hair over the long term and may promote hair growth through certain pathways	Wang et al.
Involvement and mechanism of bone marrow mesenchymal stem cells (BMSC) and conditioned medium (MSC-CM) in regulating hair follicle proliferation and regeneration	Tandem mass tag (TMT)-based quantitative proteomics		Human/ DPCs	Highlighted the significance of Krt25, CPM, STMN1, and Mb playing a role in inducing hair follicle transformation	Zhang et al.
LLLT led to significant upregulation of 11 proteins and downregulation of two proteins in DPCs	Proteomics		Human/ DPCs	Extracellular matrix (ECM) formation contributes to the clinically observed improvements in DPC area and hair diameter	Panchaprateep et al.
Increased insulin resistance exacerbates scalp microvascular insufficiency in AGA Patients	Blood metabolomics		Human/ Blood	Blood lipid increase and the development of AGA may be significantly influenced by insulin resistance	Kim et al.
Significant differential expression of all-trans retinoic acid and linoleic acid, among others, after tempeh intervention	Blood metabolomics	UPLC/Q-TOF-MS technology	Mouse/ Blood	Tempeh primarily affects metabolic pathways related to linoleic acid and amino acids, which are intimately connected to hair growth	Zhou et al.
Significant changes in various amino acid pathways dominated by tyrosine following finasteride treatment	Urine Metabolomics	liquid chromatography-mass spectrometry (LC-MS)	Human/ Urine	Disorders in amino acid-related pathways may play a role in the pathogenesis of AGA	Lee et al.

Table 2
Differential expressions of AGA identified in genomic and transcriptomic studies.

Technology	differentially expressed transcripts (DETs) or genes (DEGs)
Genomics	**Upregulated genes:** *PTGER2, KRTAP1-5, C13orf15, AXIN2, KRTAP2-4, CLEC1B, KRTAP1-4, SLC16A6, APCDD1, LEF1, DKK1, KRT81, PDZRN3, NKD1, KRTAP2-1* **Downregulated genes:** *LOH3CR2A, FGF7, EVI2A, EVI2B, KGFLP2, KGFLP1, LMCD1, FGF7P2, CCDC102B, AKR1C3, LOC644714, PPP1R3C, ADA, PTGFR, NR0B1*
Transcriptomics	**Up-regulated genes:** *IQGAP1, ROCK2, HIF1A, ROCK1, ITGB1, AKT3, DCN, CAMK2D, PTPN11, WNT5A, RAF1, EIF4B, CTSL, FZD1, TGFB1, MAP2K2, SDC2, FGFR1, ACTG1, GPC1, CCND1, EGFR, FLNB, TWIST1, FN1, CDKN1A, ITPR3, ITGA5, ACTB, FLNA, HSPG2, SDC1, MOG, CDKN2B, ICAM-1, PSMA2, PMP22, PPP1CA, TFDP1, TPH, TMF1, PKD1, AKT, Pax-5, GSTT1, SULT1E1, CD51, STAT1, CDK10, TLR s, PTGS, EGRs, AREG, HSPA1B* **Down-regulated genes:** *CD44, FGF2, PPP1CB, LUM, TIMP3, CD63, CTNNB1, CAV1, CDC42, VEGFA, ITGB5, FZD2, AKT1, MSN, WNT5B, DDX5, PRKCA, MAPK1, ARHGEF12, TIMP-2, MCL-1, IL-6 (IFNβ2), TYRO3, GPx-2, RhoB, VEGF-C, NUCB1, ACTB, CDK6, PURA, MCAM, FGR, MAP2K3, MK2, PTMS, RhoGDIα*

Table 3
Different expressions for AGA identified in proteomic studies.

Technology	different expressed transcripts (DETs) or genes (DEGs)
Proteomics	**Upregulated genes:** *MOG, CDKN2B, ICAM1, PSMA2, PMP22, PPP1CA, TFDP1, TMF1, PKD1, V-AKT 1, PAX5, GSTT1, DCN, CD51, STAT1, CDK, DRPLA, NT5, CDKS 5, HSP70, PSME2, TYB4, RAD23A, HNPCC, ROBO1, Prx 2, MAT1, DNASE2, GST-PI, MHC, DDIT4, COMT, ASS1, PAICS ADE2, CKAP4, GSN, IQGAP1, PLEC1, SPTAN1*[4,28] (in Human) Casp4, Rab3b, Hspa9, Psmb7[29], Krtap 16-1, Krt27, Krt25, Padi1, Krt28, Tyrp1, Cpm, Dct, Fbp1, Slc7a1, Mt2, Calhm5, Slc39a10, Pdcd11, Fhl2, Cux1, Mab21I4, Lrrc15, Casp14, Ctps1, Znf185, Uhrf1, Tgm3, Flg, Cbs, Acsm3, Padi3, Cdk1, Tyms, Polr2j, Lypd5, Ncaph, Stmn1, Cntfr, Edf1, Ass1, Mki67, Rnaset2b, Sap30bp, Cwc22, Ggt1, Eif1b, Tut7, Nasp, Bdh1, Mbd3, Ncapd2, Hopx, Eif1ad, Mcm3[30] (in C57BL/6 mice) **Downregulated genes:** *TIMP2, BCL2, IL6, TYRO3, GPX2, RHOA, VEGF, NUCB1, ACTB, CDK 6, PURA, MCAM, FGR, MAPK 3, MAP2K2, ARHGDIA, COL4A2, CAPN2, RAB5A, IL-4, ID2, CTGF, KRAS, RBL2, MYB, TIAM1, ESCC, CCND1, TNF-α, PSMF1, TGF-β, CDC25B, BDNF, CYP450, NM23A, RAF-1, RAR, CAD11, CXCL5, FLT3, PPP3CA, GST, RTK, MARK3, NRAS, FOSB, CRABP2, ETS-1, INHBA, ELK-1, PL4P, ETV6, IGFBP-3, PIP5K1B, D6W556, SERPINA5, PIM1, NR2F6, BMP-2, NR1D1, KSR, EPHA3*[4] (in Human) Eno1, GDI, Rplp0, Hsp60, CR1, Pgam1, G6pdh, Anxa2[29], Ankrd2, Scara5, Cox7a1, Ndst2, Mb, Hspb7, Bckdha, Ptgs1, Trappc3, Fbp2[30] (in C57BL/6 mice)

single-nucleotide polymorphisms associated with AGA [34]. Sabrina et al. conducted gene-based and single-variant analyses of exome sequencing data from a large cohort of 72,469 men to investigate the contribution of rare genetic variants to the development of MPHL, and identified five significant genetic associations and provided further support for previously implicated genes such as *EDA2R* and *WNT10A*

while also discovering new risk genes such as *HEPH*, *CEPT1*, and *EIF3F*. Additionally, genes related to MPHL are now considered to be pathogenic genes within a single gene triad, expanding the spectrum of alleles associated with MPHL and offering insights into its pathologic biology [35]. GWAS have also indicated the potential involvement of WNT signaling in AGA [36].

4.1.2. AR gene polymorphisms

Ghassemi et al. examined the impact of *AR* gene polymorphisms on the effectiveness of finasteride treatment in addressing AGA using the number of GGC sequences as a potential predictor for AGA. These authors' findings indicated that a lower number of GGC sequences was correlated with faster disease improvement, increased patient satisfaction, and enhanced response to finasteride [37]. Conversely, Arteaga-Vazquez J et al. reported no significant disparities in AR haplotype frequencies between individuals with or without AGA. This conclusion was drawn from a comprehensive sequencing analysis of multiple families, leading the scientists to propose that AGA was a multifactorial condition influenced by various factors rather than the result of a single gene mutation [38].

4.2. Transcriptomic studies of AGA

In 2021, Zhang et al. generated an initial global transcriptomic analysis of DPCs in both 2D and 3D co-culture models following DHT treatment, and ascertained that the 3D co-cultured DPCs offered a more accurate representation [39]. We summarize in Table 2 the DETs or DEGs in AGAs as obtained by transcriptomic analysis, and in Fig. 1 we depict the relevant pathways (dominated by the Wnt pathway) involved in the differential expression of transcripts in transcriptomic studies.

4.2.1. Microarray technology

Miao et al. uncovered a significant upregulation of key inflammation regulators in the AGA transcriptome [40]. RNA microarray analysis of plucked hair follicles also revealed for the first-time ever that three ion channel markers (*LRRC26, KCNK5*, and *B3GNT3*) were downregulated in AGA [41]. Karnik et al. identified the Notch signaling pathway as a major disrupted pathway in AGA through microarray research and highlighted the *JAG1* gene as a susceptibility locus for AGA in males [42].

Studies of human hair follicle tissue have indicated that *WNT10A* may play a functional role in the development of AGA. Philpott et al. observed an increase in the levels of the Wnt pathway inhibitor pigment epithelium-derived factor (*PEDF*) and secreted frizz-related protein 1 (*SFRP1*), providing further evidence for a role of Wnt inhibition in AGA [43]. Reports revealed an inhibition of *WNT3* and *HSD17B6* genes in AGA through microarray expression analysis of biopsies and DNA methylation [44]. Similarly, Dey et al. executed differential gene ontology enrichment analysis to identify apoptosis, cellular proliferation, disorganized neuronal pathways, and WNT signalling as important factors in the alopecia process [45]. Genes associated with Wnt/β-linked protein and bone morphogenetic protein/transforming growth factor β signalling pathways were also demonstrated to be downregulated in AGA [46].

4.2.2. RNA sequencing

Premanand et al. identified 32 DEGs in their study and used the ReactomeFIViz application to build a protein-functional interaction network of these DEGs. The analysis by these authors revealed that downregulated DEGs were associated with Wnt and TGF signaling, while upregulated DEGs were linked to oxidative stress-related pathways [47]. It has been reported that Wnt signalling plays a role in inducing hair growth in DPCs through the β-catenin pathway that is

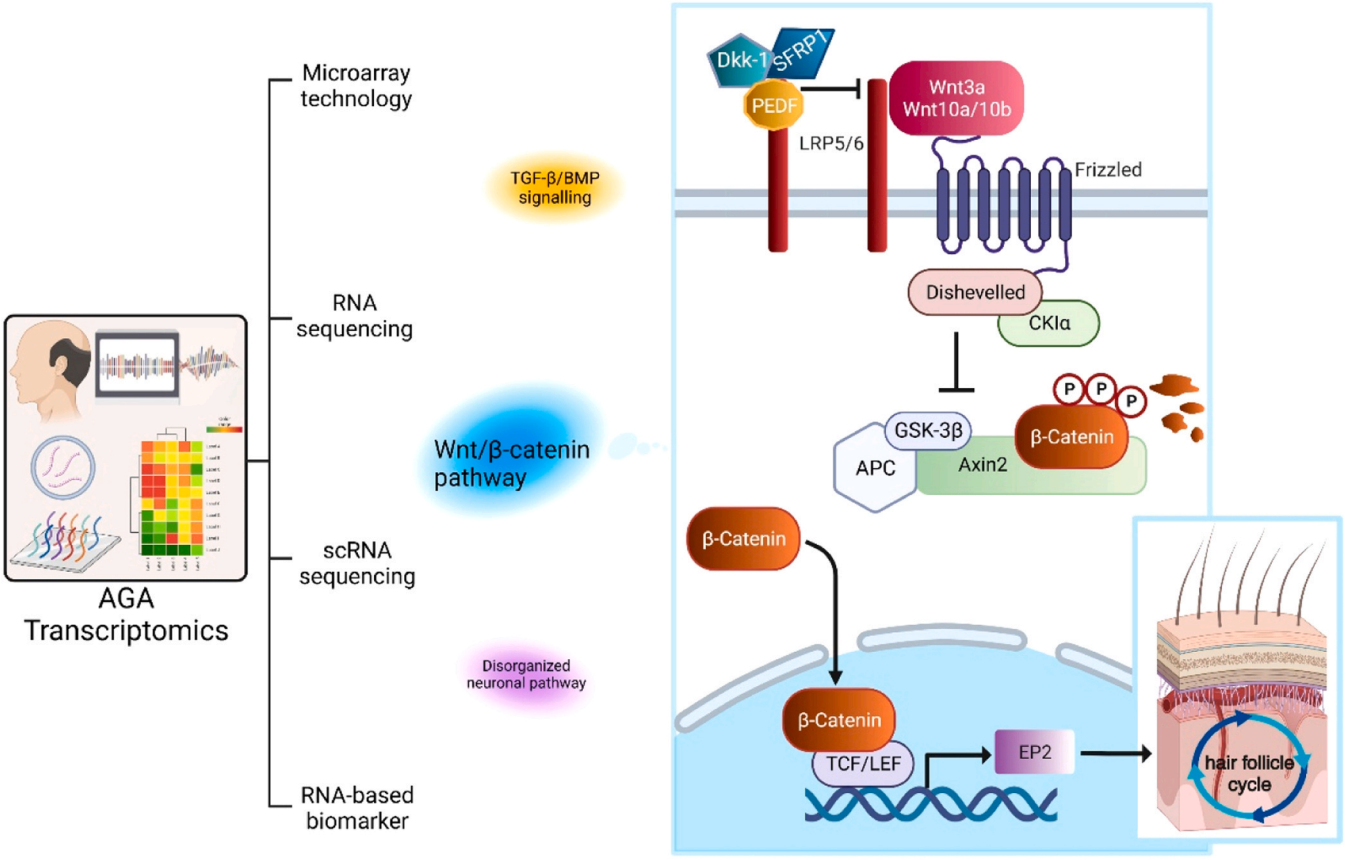

Fig. 1. Transcriptomic data establishes a connection between Wnt signaling and the hair cycle.

sustained during the growth phase [48–50]. Shin et al. conducted a series of studies on *Wnt3a* regulatory genes using various techniques such as immunofluorescence staining, microarray, RT-PCR, and western blotting, and identified target genes of the Wnt/β-catenin pathway, observing that inhibitors (*AXIN2, DKK-1*) and activators (*LEF1, FZD7*) were upregulated after Wnt3a treatment [51]. By increasing *EP2* expression in DPCs, hair growth may be promoted by regulating its activity via autocrine/paracrine mechanisms [52]. Chew et al. analyzed the transcriptome profiles of apical occipital follicular units (FUs) using RNA sequencing, and demonstrated that upregulated genes were predominantly involved in lipid synthesis and electron carrier activity/-transport. Through RT-qPCR validation, these researchers confirmed five upregulated genes (*CYB5R3, FADS2, PTGDS, SDHA,* and *SRD5A1*) that exhibited a consistent trend with the RNA-Seq data [53], and also obtained immortalized human DPCs from both alopecic and non-alopecic scalps to identify AGA risk genes. They ascertained that genes downregulated in alopecic scalps were associated with gene-ontology clusters related to blood vessels, cell motility, cell migration, cell death, phosphate metabolism, and protein kinases when compared to non-alopecic scalps; and they suggested that the diminished presence of DPCs in balding scalps may impede the formation of blood vessels around hair follicles, potentially contributing to the development of AGA [54].

Low-level laser therapy (LLLT) was officially approved by the FDA for the treatment of andropause in 2007, with the currently approved laser wavelengths for the treatment of andropause being 655 nm, 678 nm, and 650 nm [55]. Yang et al. demonstrated that 650-nm red light effectively delayed the transition of the hair growth cycle from growth to degeneration in vitro. Their transcriptomic analysis using RNA-Seq and gene clustering revealed 410 upregulated transcripts and 318 downregulated transcripts, indicating that 650-nm wavelength red light stimulation enhanced hair follicle growth by influencing biologic processes such as leukocyte transendothelial migration, metabolism, and adhesion [56]. These results also provided additional evidence for the involvement of Wnt signaling in both AGA and LLLT treatments. Real-time PCR results by others showed that 650-nm red light treatment upregulated genes involved in the Wnt signalling pathway, including Wnt10b and β-catenin [57]. Qu et al. compared transcriptomic sequencing results between the forehead and posterior occipital region of AGA patients, describing 214 DEGs and 511 DEGs, respectively, when comparing AGA patients with healthy individuals. These DEGs were primarily associated with human infectious diseases and microenvironmental signalling pathways, particularly those linked to DNA damage, oxidative stress response, and extracellular matrix assembly according to the Gene Ontology Consortium database [58].

Some studies have shown that 3D spherical culture could partially restore the full transcriptional characteristics of DPCs [59,60]. In 2021, Zhang et al. compared the AGA-related genes and pathways between 2D and 3D cultured DPCs with DHT treatment under high-flux RNA-Seq, and uncovered 501 overlapping DEGs, 10 key genes, chemokines, and related pathways in DPCs cultured in the two models, indicating that chemokines and IL-17 pathways may be related to AGA. More importantly, this study provided the first-ever global transcriptome of DPCs in 2D and 3D co-cultured models with DHT treatment [39].

4.2.3. Single-cell sequencing

The advancement of high-throughput sequencing technology has led to a comprehensive understanding of intricate biologic processes, and single-cell sequencing technology has further improved the analysis of cellular heterogeneity in complex tissue structures [61].

Novel single-cell sequencing results linked abnormal hairiness in AGA to oxidative stress [62]. Research suggests that ATF3 and NAPA may suppress oxidative stress-related pathways in AGA progression, while CRABP2 and UBE2D3 could affect the hair follicle cell cycle, leading to apoptosis and growth inhibition [63]. These discussions laid the foundation for further exploration of the pathophysiologic mechanisms and clinical interventions for AGA.

Ge et al. utilized single-cell RNA sequencing (scRNA-Seq) technology to analyze samples from three stages of hair follicle development: induction, organogenesis, and cytodifferentiation. They delineated the lineage differentiation trajectory of dermal and epidermal cells, accurately describing the gene-expression profiles of hair stem cells and inner hair root sheath (IRS) [64]. Their research offered valuable insights into the heterogeneity of DPCs during hair follicle development.

4.2.4. Noncoding RNAs

4.2.4.1. MiRNAs. MiRNAs, which are short noncoding RNAs consisting of 19–22 nucleotides, interact with the three prime untranslated regions (3'-UTRs) of specific messenger RNAs (mRNAs) to regulate gene translation [65]. Bryan et al. conducted a comparison of transcriptomic profiles between normal and miniaturized hair follicles in AGA and between normal male parietal and occipital regions, and discovered that hormone receptors other than retinoid receptors—particularly those in the PPAR pathway—were critical to follicle miniaturization. Furthermore, miRNA analysis revealed that miRNA target genes were enriched in retinoid receptors, PPARGC1α/PPARγ signaling, and antigen-presentation pathways [66]. For example, Liu et al. identified 506 mRNAs and 55 microRNAs that were differentially expressed in AGA vertex hair follicles (HFs) through transcriptomic analysis [29]. Additionally, patients with AGA displayed a specific miRNA expression profile, with abnormal expression of miR-133b potentially leading to inactivation of the Wnt/β-catenin pathway, thereby regulating hair growth [67]. A study by Mohammadi et al. demonstrated that miR-324–3p regulated the signaling of mitogen-activated protein kinase (MAPK) and transforming growth factor (TGF) enzymes to facilitate the differentiation and migration of cultured keratin-forming cells [68]. Xu et al. investigated signaling molecules and miRNA expression profiles based on mouse hair cycle construction and proteomics results (refer to 4.3 Proteomics technologies in AGA for details), and ascertained that compared to telogen, miR-690, obsolete-49, and miR-1308 were upregulated, while miR-291a-5p and miR-212 were downregulated during anagen. In catagen, the expression of miR-690 and obsolete-49 was upregulated, whereas miR-127–3p and miR-212 were downregulated [69]. Previous studies have depicted a strong correlation between these specific miRNAs and various diseases such as alcoholic liver disease, breast cancer, and ovarian cancer. However, additional research is necessary to elucidate the regulatory functions of these miRNAs in the hair cycle [70–73].

4.2.4.2. LncRNAs. More than 80 % of noncoding RNAs are long noncoding RNAs (lncRNAs) that are crucial to the regulation of protein-coding genes through various mechanisms, including the formation of stable triple-helical complexes by binding to DNA bases [74]. Bao et al. conducted a pioneering study on lncRNAs associated with AGA, and identified alterations in lncRNAs and their target genes that could potentially serve as novel targets for the prevention and treatment of AGA [75]. Liang et al. used high-throughput sequencing to analyze gene expression in patients with moderate and severe AGA, identifying 284 upregulated and 421 downregulated genes in the areas of hair loss and non-hair loss. Analyses of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) revealed the differential expression of mRNA genes and lncRNAs, pinpointing genes such as *IER3, FOSB,* and *ATF3* as potential AGA susceptibility genes or DEGs in specific brain regions. Additionally, 216 metabolic pathways were identified, including TNF signaling, RNA degradation, and influenza A. Liu and co-workers also identified 127 differentially expressed noncoding RNAs in vertex hair follicles from patients with AGA, linking pathways such as hypoxia inducer factor-1, Wnt/β-catenin, and focal adhesion to HIF-1 expression. Their study additionally verified the differential expression of HIF-1 proline hydroxylase (EGLN1, EGLN3) and WNT/ β-catenin

pathway inhibitors (SERPINF1, SFRP2) [29].

4.2.4.3. CircRNAs. Circular RNAs (circRNAs) are abundant in the human body and are significant in the development and advancement of various diseases. Despite this, the precise contributions of circRNAs to AGA remain largely unexplored. Through an extensive examination of circRNA expression patterns that exploited whole-transcriptome sequencing, we identified circAGK as a promising target for focused therapeutic strategies in AGA [30] (see Fig. 2).

4.3. Proteomics technologies in AGA

In contrast to genomics or transcriptomics, Proteomics is closely linked to phenotyping and has emerged as a potent tool for investigating biomarkers related to AGA. Analysis of proteomic data in skin diseases has revealed enriched pathways related to cell death, metabolism, bone, immunity, and inflammation [76].

4.3.1. DPC-based proteomic biomarkers

DPCs are recognized for their pivotal role in the regulation of hair growth and loss [77–80].

Xia et al. implemented proteomic techniques to compare DPCs with and without aggregation characteristics, and pinpointed heat shock protein 70 (HSP70) and mitochondrial ribosomal protein S7 (MRPS7) as contributors to the aggregative behavior of cultured DPCs. This finding lays a solid groundwork for elucidating the molecular mechanisms underlying DPC aggregation [81]. Additionally, these researchers observed an overexpression of seven metabolic enzymes, neuropeptide H3, and annexin A2 in the aggregated DPCs.

4.3.2. Proteins associated with the hair cycle and regulation of follicle growth

Williams et al. used proteomics to demonstrate an increase in dermal envelope proteins in the secretome of aging dermal fibroblasts [82]. In another proteomic analysis, the differential expression of hair follicle cycle-related proteins was explored, and the authors identified 44 differentially expressed proteins (DEPs) of 95 protein spots. These proteins play roles in Ca^{2+}-regulated biologic processes, migration, and signal regulation [28]. Xu et al. applied two-dimensional electrophoretic separation, mass spectrometric identification, and protein-database retrieval to identify 45 of 95 DEPs related to apoptosis, cell proliferation and differentiation, and cell signaling. Specifically, lamin A/C, annexin A1, GAPDH, EF1, CAMK II, MLC, and TPM 1 were upregulated in the growth phase, while CYTb was upregulated in the regression/-quiescent phase. These investigators also conducted transcriptomic analysis to investigate the miRNA expression profile [69] (see 4.2 Transcriptomic technologies in AGA for details). Won et al. employed shotgun proteomics and network analysis to identify 28 types of DPC-specific extracellular matrix proteins, including transporters (ECM1, A2M), enzymes (LOX, PON2), and polypeptidases (C3line C1R). ITGB1, IGFBP3, and THBS were subsequently selected as potential biomarkers of hair growth-regulating proteins [83]. Wang et al., using proteomic and bioinformatic data, found that annexin A1, vimentin, and lamin A/C were dynamically upregulated in hair over an extended period, potentially promoting hair growth by enhancing migration, mitosis, cell-dynamic balance, and gene regulation. Cluster analysis

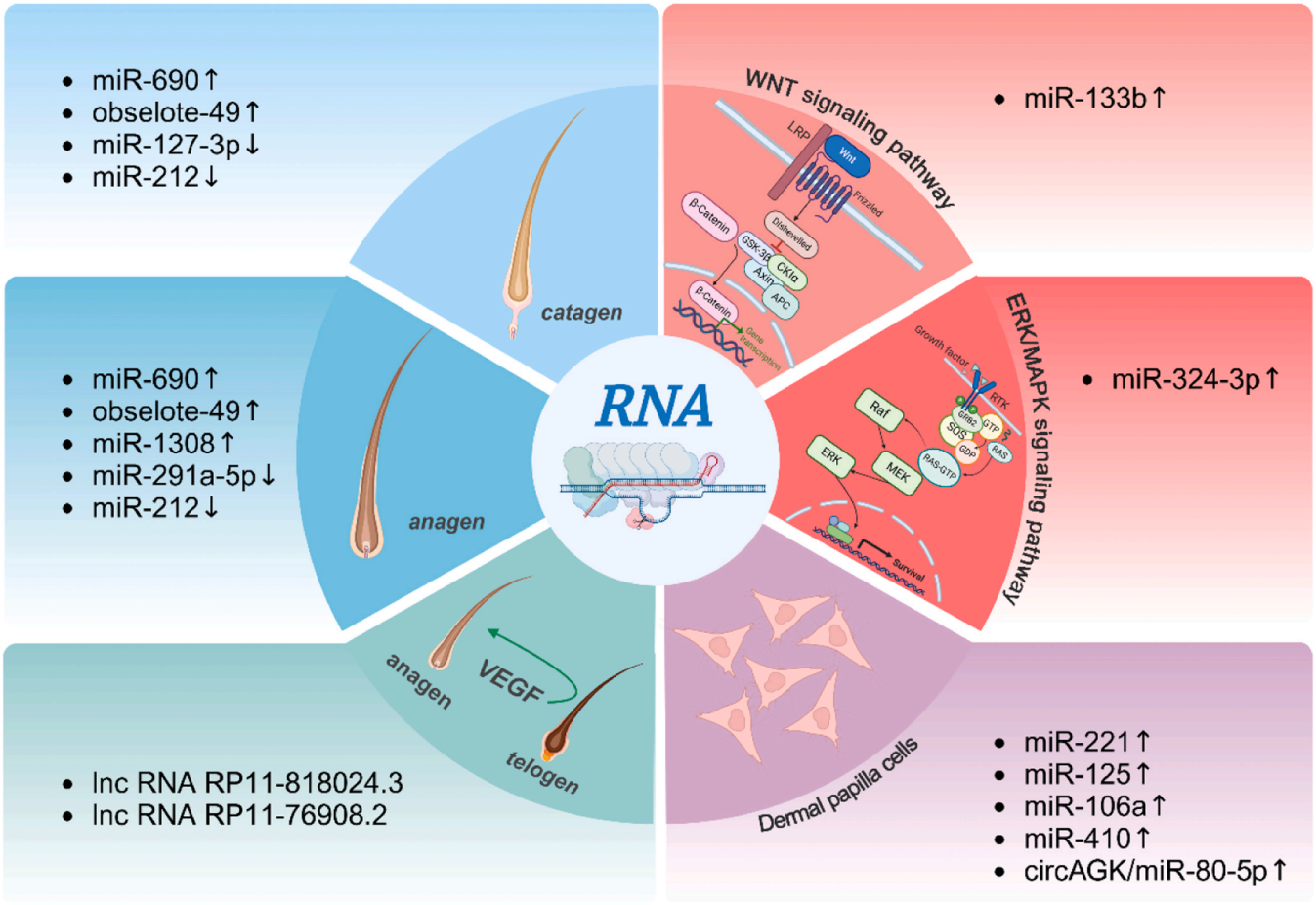

Fig. 2. Differentially expressed non-coding RNA in AGA. The different perspectives of the hair follicle cycle, vascular endothelial growth factor (VEGF) involved in the hair follicle cycle, related pathways, and dermal papilla cell (DPC)-related differential expression are demonstrated, respectively.

unveiled distinct protein-expression patterns at various stages of the hair growth cycle, encompassing apoptosis, proliferation/cell survival, regulation of signal transduction, cell phase transition, mitosis/cytokinesis, and secretion [28].

Zhang et al. conducted a study to investigate the involvement and underlying mechanisms of bone marrow mesenchymal stem cells (BMSC) and conditioned medium (MSC-CM) in regulating hair follicle proliferation and regeneration. Adopting tandem mass tag (TMT)-based quantitative proteomics analysis, these investigators explored the protein-protein interaction network. Their results highlighted the significance of Krt25, CPM, STMN1, and Mb as playing a role in inducing hair follicle transformation. Stmn1, Ncapd2, Krt25, and Ctps1 were specifically identified as key components within this network [84].

4.3.3. *DEPs for AGA therapy*

LLLT therapy has recently gained attention as a potential complementary or alternative treatment in clinical practice [85,86]. Panchaprateep et al. completed a study showing that LLLT led to significant upregulation of 11 proteins and downregulation of two proteins in dermal papilla cells (DPC) compared to baseline[87]. These proteins are involved in various biologic processes such as cell transcription, protein biosynthesis, cell energetics, lipid homeostasis, extracellular matrix (ECM) formation, ECM structural components, cell adhesion, and angiogenic regulation[87]. Importantly, the increased expression of key ECM proteins contributes to the clinical improvement observed in the DPC area and hair diameter.

4.4. *Metabolomic technologies in AGA*

Multiple studies have revealed a strong correlation between AGA and dyslipidemia [25,26], and we describe current metabolomic studies of AGA from a targeted versus untargeted perspective in Fig. 3.

4.4.1. *Targeted metabolomics*

Wang et al. discovered that 158 characteristics were downregulated and 138 characteristics were upregulated due to psychological pressure [24]. The analysis of secondary metabolites using KEGG highlighted D-glucose-6-phosphate as the most significantly reduced metabolite, suggesting that glycolytic metabolism may be important in the inhibition of hair growth. With this study, the investigators elucidated the molecular mechanism by which psychological pressure impeded hair growth, and laid a theoretical foundation for targeting specific pathways in alopecia treatment. Transcriptomic analysis [88] identified 97 metabolic-related genes, with differential expression in various pathways such as arachidonic acid metabolism, glutathione metabolism, glycolysis, nicotinic acid and nicotinamide metabolism, purine metabolism, retinol metabolism, and the ABC transporter pathway. Consequently, lipid metabolism is considered to be crucial in maintaining normal functioning of cells and is linked to hair development and function.

4.4.2. *Nontargeted metabolomics*

4.4.2.1. Blood metabolomics. A blood metabolomics analysis indicated higher levels of myristic acid, oleic acid, total unsaturated fatty acids, and total fatty acids in patients with AGA compared to normal controls [88]. This study highlighted the vasoconstriction due to increased insulin resistance as worsening scalp microvascular insufficiency in AGA patients. Kim et al. proposed that insulin resistance might therefore exert significant actions in AGA development and in the elevation of blood lipids [89]. Animal models of AGA serve as an invaluable tool in the testing of new therapeutic targets for the treatment of AGA, thereby accelerating the process of intervention or therapeutic drug discovery [90]. Another study that entailed UPLC/Q-TOF-MS technology to analyze serum metabolic profile changes in AGA mice after treatment with finasteride and tempeh solution identified differential expression

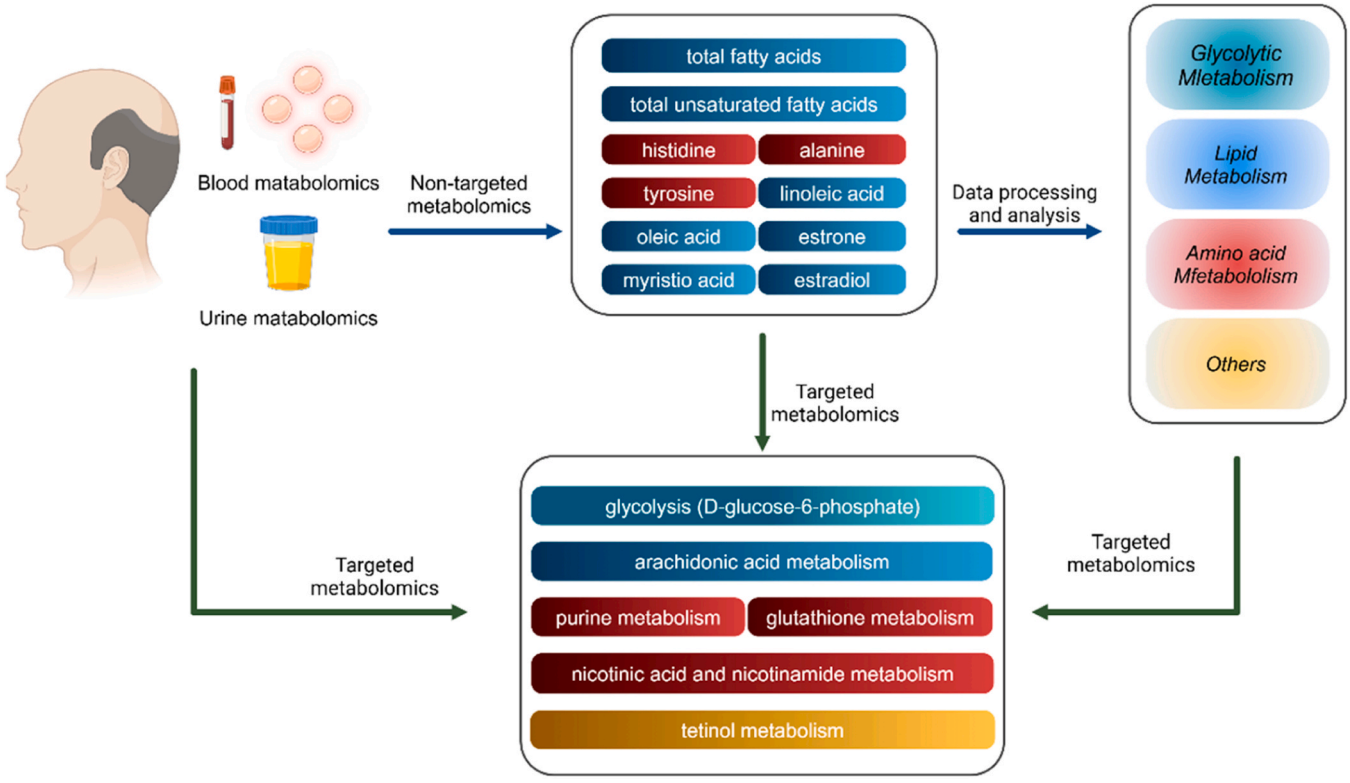

Fig. 3. Metabolomics reveals disease-related metabolic molecules. Differently expressed metabolites and the pathways involved can be identified by untargeted metabolomics for comprehensive data collection and further quantitative analysis and validation by targeted metabolomics, and the combination of the two approaches can provide a complete framework for the study.

markers such as all-trans retinoic acid and linoleic acid, displaying potential alterations after tempeh intervention. By leveraging the HMDB and KEGG databases, these researchers discerned that tempeh primarily influenced metabolic pathways associated with linoleic acid and amino acids. These authors identified expression patterns and pathways that were closely associated with hair growth, and this laid the groundwork for further research on using tempeh as a treatment for AGA [91].

4.4.2.2. Urine metabolomics. Lee et al. executed liquid chromatography-mass spectrometry (LC-MS) and uncovered significant changes in various amino acid pathways dominated by tyrosine after finasteride treatment[92]. These results imply that disruptions in amino acid-related pathways are critical in the development of AGA. Moreover, this study revealed similar alterations in estrone and estradiol levels in urine samples when compared to serum, plasma, and cerebrospinal fluid, providing initial evidence of estrogen-modulation as a consequence of post-finasteride syndrome. Additionally, the researchers observed a reduction in the DHT/T ratio in human urine samples, which acts as an indicator of finasteride's effectiveness [92,93].

5. Multi-omics and systems biology

5.1. Integrative analysis of AGA using multi-omics tools

Single omics such as genomics, transcriptomics, proteomics, or metabolomics can be integrated using the Venn diagram to identify and display common biomarkers across the group of analytic tools. However, solely focusing on a single molecule or a single omics analysis is not sufficient to allow full elucidation of the complex regulatory network composed of different types of molecules. Therefore, a comprehensive analysis of multiple omics is essential to achieve a more thorough understanding of the pathogenesis and treatment of AGA.

Genomic studies in AGA have revealed variants linked to AR genes, as well as genes related to hair follicle growth and function (including those in the Wnt pathway and cortisol metabolism). Through gene-expression profiling, researchers have pinpointed genes such as hair follicle growth factor and molecules involved in angiogenesis that show altered expression in individuals experiencing hair loss. Additionally, investigations involving knockout or overexpression of specific genes both in vitro and in vivo have facilitated identifying genes associated with hair loss and in understanding their impact on hair follicle growth.

Transcriptomic studies have identified key pathways such as androgen signal transduction, cellular proliferation, and apoptosis that are crucial in alopecia. These studies have also assisted in predicting and identifying biomarkers for AGA, thus providing valuable insights in the development of targeted therapeutic strategies.

Proteomics studies have further revealed significant changes in protein expression in alopecia patients, particularly in proteins related to hair follicle growth, apoptosis, and inflammation. Metabolomics research in AGA has the potential to uncover metabolic markers and pathways that shed light on how androgens impact hair follicle cell metabolism, offering opportunities to enhance hair growth through targeted regulation of specific metabolic pathways or metabolites.

5.2. Diagnostic and therapeutic approaches combined with omics tools

Genomic data can be used to identify genetic variants linked to AGA so as to evaluate an individual's susceptibility to the condition, while transcriptomics can be employed to analyze gene-expression variations, pinpoint crucial genes and pathways, and characterize AGA biomarkers using techniques such as RNA sequencing [94].

From a therapeutic perspective, genomics can be implemented to discover new drug targets and develop novel therapeutic methods through association studies. Additionally, genomics can be employed to predict individual responses to different treatment plans by analyzing differential expression before and after treatment using transcriptomics. This allows for the formulation of personalized treatment plans and the improvement of therapeutic efficacy. Examples include the use of CRISPR/Cas9 technology to repair or modulate genetic variants associated with AGA [95]; predicting a patient's response to conventional drugs (e.g., finasteride or minoxidil) based on his or her genomic data to select the most effective treatment regimen[96]; or developing small molecule drugs that target the gene or pathway based on transcriptomic data[97].

Protein markers can be identified to track the effectiveness of treatments and prognoses, and the impact of medications on protein expression can elucidate their underlying mechanisms of action [98]. For example, blood tests for these markers can identify AGA in the early stages of hair loss, thereby enabling timely therapeutic intervention [11].

Finally, metabolomics-driven intervention strategies may be employed as supplementary therapies for AGA. Certain vitamins and minerals, for example, have been identified as being deficient in individuals with AGA, and supplementation with these nutrients has been shown to improve hair health [99,100].

It is important to note that regular examination of omics data can also be used to monitor disease development and treatment efficacy in real time, which can inform changes to treatment regimens. Integration of multi-omics data can therefore provide an assessment of overall disease status and response to treatment.

5.3. Combined application of multi-omics and systems biology

The integration of transcriptomics and proteomics offers a valuable approach to elucidating the intricate relationship between gene expression and protein expression, enhancing our understanding of the molecular mechanisms underlying AGA. Through the analysis of transcriptomic and metabolomic data, significant changes in metabolites and metabolic pathways associated with AGA can be identified, offering crucial insights into the metabolic processes involved in AGA. Investigation of proteomics and metabolomics enables the identification of interactions between AGA-related metabolites and proteins, and this facilitates a deeper understanding of the metabolic regulatory mechanisms in AGA. Adopting a multi-omics approach allows for the construction of a comprehensive molecular network that elucidates the complex interplay among gene expression, protein expression, and metabolism in the development of AGA. This integrated analysis can then lead to the discovery of novel biomarkers and potential therapeutic targets, paving the way for the development of more effective treatment strategies.

Omics modalities currently offer a limited amount of biologic information. To achieve a more profound understanding of disease data and to identify potential diagnostic or therapeutic targets, it is essential to merge clinical data with bioinformatics. This integrative approach allows the exploration of various molecular interactions and changes both upstream and downstream. Systems biology is pivotal in this endeavor as it aids in the study of molecular interactions at the cellular level and tissue interactions at the organ level by integrating the available data.

6. Challenges to integrative omics analyses

Despite the significant potential of multi-omics in AGA research, several challenges need to be addressed[101]. First, the sheer volume of genomic, transcriptomic, proteomic, and metabolomic data generated by multi-omics studies poses a significant challenge in terms of efficient processing, analysis, and integration so as to extract relevant biologic information and interrelationships. Second, the requirement for a large sample size in multi-omics studies in order to achieve statistically significant results can be hindered by difficulties in collecting high-quality samples, particularly in conditions such as AGA where patient sample

collection may be challenging. Moreover, interpreting the massive amount of biologic information from multi-omics studies and linking it to disease pathogenesis remains a challenge. Lastly, standardizing and improving the consistency of technical platforms and experimental methods used in multi-omics research is essential[102–104]. And addressing data privacy concerns and ethical issues also presents important hurdles[105].

6.1. Influence of different culture methods

Although omics studies at the cellular level have shown that disparate cell culture methods can influence the expression of specific genes or proteins, multi-omics studies can in contrast provide corresponding results at various levels. Three-dimensional cell culture technology, using scaffolds or specialized devices, is an innovative approach that mimics the in vivo growth state of cells, and can establish a more reliable foundation for clinical research [106]. Evaluating and verifying the effects of different culture methods at a macro level (which closely mimics in vivo conditions) enables the simulation of the actual rhythm of cellular proliferation and apoptosis. This, in turn, establishes a more robust basis for fundamental research, such as understanding disease pathogenesis.

6.2. Technical challenges to omics

High-throughput sequencing technology enables a comprehensive and detailed analysis of the genome and transcriptome of a species. Compared to first-generation Sanger sequencing, it offers significant advantages in handling large samples, making it a core technology in current omics research [107].

Transcriptomics possesses significant technological advantages in certain areas. RNA-Seq requires a smaller sample size and can be executed to analyze RNA extracted from trace tissue or single-cell samples, whereas proteomics typically necessitates larger sample sizes for effective and efficient protein identification and quantification [108]. While transcriptomics typically entails only RNA extraction, proteomics requires more complex sample preparation. RNA-Seq is capable of measuring the expression levels of thousands of transcripts simultaneously, whereas proteomics requires complex mass spectrometry for protein identification and quantification [109]. The data-analysis methods for transcriptomics are relatively mature, including standardized analysis pipelines and extensive database support. The analysis of proteomics data is more complex than that of transcriptomics data, requiring multi-step mass spectrometric data processing and protein identification [110–112]. However, studies on yeast and mammalian cells have demonstrated that there is no direct correlation between mRNA abundance and protein levels [113,114]. Consequently, while transcriptomics reflects clear advantages in terms of data output speed, sample processing, data analysis, cost-effectiveness, and sensitivity, proteomics is irreplaceable in protein function studies and post-translational modification analysis. Researchers have identified a clear preference for the combined study of the transcriptome and proteome, given their close relationship as upstream and downstream components. The integration of the two approaches can facilitate the acquisition of more comprehensive biological information and a more nuanced understanding of the system as a whole.

Omics studies have delved into the differential expression in patients with AGA from multiple angles, including genes, transcription, proteins, and metabolism. These studies have also been applied to assess the effects of established medications on the disorder and the potential for symptom reversal. By leveraging the unique strengths of various omics approaches, these studies provide valuable insights. Nevertheless, the connections between these disparate approaches and the molecular pathways responsible for androgen-related effects remain largely uncharted territory, necessitating additional research.

7. Future perspectives

AGA is a common hair-loss disorder influenced by genetic, endocrine, and mental factors; and the pathogenesis of this disorder cannot be fully elucidated by studying individual biomolecules alone. Therefore, integrating research data from various sources and platforms has constituted a reliable approach in basic medical research [102]. Genomics, transcriptomics, proteomics, metabolomics, and bioinformatics analyses have been exploited to analyze abnormal expression patterns in the AGA, identifying key signal transduction pathways. However, it is insufficient to explain the complex biological processes of diseases solely from a single omics perspective [115]. Therefore, joint research involving transcriptomic and proteomic analyses are becoming increasingly prevalent, reflecting a shift toward collaborative research efforts. Multi-omics analyses thus allow for a comprehensive understanding of differential expression, identification of genes or proteins regulated by post-transcriptional mechanisms, and the discovery of crucial regulatory pathways. Omics techniques have significantly advanced the understanding of molecules and pathways involved in AGA. Genomic studies have confirmed the multifactorial nature of AGA, rather than being attributed to a single mutated gene. Transcriptomics has elucidated the therapeutic mechanisms of action underlying 650-nm light in AGA treatment and highlighted the differential expression of biomarkers in key pathways such as TNF- and Wnt/β-catenin-signaling pathways and oxidative stress. Proteomic approaches have pinpointed factors involved in apoptosis, proliferation, and hair follicle transformation in AGA patients. And metabolomics has uncovered alterations in amino acid and lipid pathways linked to hair loss pathogenesis.

Integration of omics methods—including genomics and metabolomics—can establish a comprehensive interaction network that can be adopted to better comprehend the complete pathological mechanisms underlying the effects of AGA. Despite these advancements, challenges remain in multi-component analysis, emphasizing the need for robust bioinformatic tools to process and integrate diverse data types.

Of particular focus is that of next-generation phenotyping (NGP), which represents a promising avenue for the analysis and diagnosis of rare diseases, with the potential to be employed in conjunction with exome sequencing so as to facilitate the identification of disease-related patterns.

As early as 1991, Hayashi et al. developed a quantitative method for measuring hair growth using light microscopic and image analysis. These authors studied hair growth rates in alopecia areata and normal subjects, and found a significant difference [116]. In 1995, Lee et al. also proposed that computerized image analysis could be applied to measure a large number of hairs in an automated manner, and further demonstrated that computerized image analysis could be employed in clinical trials by measuring hair shaft, follicle diameter, and inner and outer root sheath area in 10 AGA patients and 10 normal controls using color image-analysis software. This approach provided a substantial amount of data and objectivity, which are essential for determining the efficacy of hair regeneration [117]. A 2014 study employing in vivo imaging and computer-assisted image analysis after manual processing (CAIAMP) revealed that, among other structural and functional parameters characterizing hair follicle degeneration, linear hair growth rate merited further investigation [118]. Bilgiç Temel et al. (2018) proposed using TrichoScan, a software program that combines standard epiluminiscence microscopy and automated digital image analysis to measure hair growth. This software can be used in clinical trials or to detect the course of treatment in patients with hair loss [119]. In 2020, Soga and colleagues proposed the use of magnetic resonance imaging (MRI) for hair and scalp analysis to assess and quantify anatomical changes of the scalp associated with AGA, and their findings demonstrated the ability of MRI to detect significant differences in objective hair counts and visual subjective assessments. The potential of MRI for hair and scalp (magnetic resonance histology [MRH]) as a novel imaging technique for the analysis of healthy and pathological scalps is now

supported, promising a new method for the quantitative objective analysis of AGA [120,121]. In the period between 2021 and 2023, Colin-Pierre and colleagues initially attempted to utilize infrared spectral imaging (IRSI) as a means of identifying the location of proteins, proteoglycans (PG), glycosaminoglycans (GAG), and sulfated GAG within hair follicles (HF) without the use of reagents or labels. From a dermatological perspective, IRSI may ultimately prove to be a promising technique for the long-term diagnosis and prevention of hair loss [122].

In 2009, Rakowska conducted a retrospective evaluation of trichoscopic images as a diagnostic criterion for female androgenic alopecia (FAGA) [123]. In 2022, Gao et al. employed trichoscopic data (including hair density and diameter distribution) as potential quantitative metrics. This led to the development of a deep-learning framework capable of accurately analyzing hair density and diameter distributions in male androgenetic alopecia, as well as a quantitative model for predicting the basic and specific types of male androgenetic alopecia [124]. In 2024, Kamishima and colleagues conducted a study of the sex-specific trichoscopic features of male androgenetic alopecia (MAGA) and female pattern hair loss (FPHL), and their findings indicated that MAGA was characterized by a gradual decrease in hair diameter, followed by a decrease in the number of hairs per follicular unit; in contrast, FPHL showed an opposite progression [125]. Additionally, a study published this year revealed that trichoscopy can be employed as a sensitive approach by experienced dermatologists to assess therapy response in patients with AGA. This approach involves determining terminal, vellus, and total hair counts (THC, VHC, and ToHC) and the terminal-to-vellus hair ratio (T/V) [126].

Moreover, an article on image analysis described reflectance confocal microscopy (RCM) imaging to study AGA at the tissue level to differentiate the stage of the disease, serving as an intermediate step between trichoscopy and histology in the diagnosis of hair disorders. Additionally, RCM covers optical coherence tomography to monitor the clinical response to hair loss treatments and to visualize hair follicles in order to improve the outcome of hair transplantation. Finally, the modality addresses software development. Optical coherence tomography can be used to monitor the clinical response to alopecia therapies and to view hair follicles, with the objective of improving the outcomes of hair transplantation. Software development is thus conducted in conjunction with trichoscopy, with the aim of measuring hair growth factors [127].

The advantages of image analysis have been previously outlined, and the integration of image analysis with omics data can markedly enhance the diagnosis, treatment, and monitoring of AGA. This multifaceted approach can provide a more detailed understanding of the disorder and facilitate the development of personalized treatment strategies. First, imaging such as dermoscopy can be employed to assess scalp and hair follicle conditions, which can then be quantified by computer analysis in order to identify follicle miniaturization and patterns of hair loss. Furthermore, the combination of image data with omics data can serve to confirm associations between gene expression and patterns or degrees of hair loss. From a therapeutic standpoint, genomic and proteomic data can be utilized to identify potential therapeutic targets and drug candidates. Image analysis can be executed to monitor hair recovery during treatment, assess treatment efficacy, and serve as a criterion for drug screening. This, in turn, will facilitate the development and optimization of novel therapies. Consequently, the concurrent collection and analysis of patient images and omics data will enable the dynamic monitoring of treatment, the assessment of treatment efficacy, and the refinement of treatment plans.

Authorship contributions

Yujie Li (First author): Drafted and revised the manuscript. Cuiping Guan (Corresponding author): Contributed to developing writing ideas and revising the manuscript. Tingru Dong: Completed drawing and modification of illustrations. Sheng Wan: Assisted with a portion of the illustrations. Renxue Xiong, Shiyu Jin, and Yeqin Dai: Helped gather references and incorporate additional content. All authors reviewed and approved the final version for submission.

Publication consent

All authors have read and approved the final version of the manuscript and agree to its submission for publication.

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CRediT authorship contribution statement

Cuiping Guan: Funding acquisition, Writing – review & editing. **Sheng Wan:** Investigation. **Renxue Xiong:** Formal analysis. **Shiyu Jin:** Validation. **Yeqin Dai:** Validation. **Tingru Dong:** Data curation, Visualization. **Yujie Li:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Author contributions

Yujie Li drafted the manuscript. Tingru Dong was responsible for the illustrations. Sheng Wan assisted with a portion of the illustrations. Renxue Xiong, Shiyu Jin, and Yeqin Dai helped gather references and incorporate additional content. Cuiping Guan contributed to developing writing ideas and revising the manuscript. All authors reviewed and approved the final version for submission.

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