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Perspective

Adrenal Aging: Region-Specific Vulnerability and Proteostatic Decline - Mechanisms, Biomarkers, and Translational Opportunities

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ABSTRACT: The adrenal gland integrates stress, metabolic, immune, and circadian signals to safeguard organismal homeostasis, yet its aging biology has been comparatively overlooked. Converging evidence from recent primate single-nucleus atlases, functional perturbations in human adrenal cells, human pathology, and multi-organ proteome aging resources reveals a coherent mechanistic picture: adrenal aging is region-specific, substrate-limited, and constrained by proteostasis, characterized by decline of dehydroepiandrosterone sulfate (DHEA-S) and aldosterone, while preserved cortisol output on average with diurnal flattening and higher prevalence of autonomous cortisol secretion with ageing. These endocrine trajectories implicate heightened vulnerability of the zona reticularis (ZR) and zona glomerulosa (ZG) versus the zona fasciculata (ZF). At the cellular level, ZR cells exhibit senescence, immune activation, and lipid metabolic disruption, including downregulation of androgen sulfation. Broad reduction of LDLR across cortex limits cholesterol import reduces DHEA-S, linking substrate scarcity to endocrine decline. Proteostatic lesions including aggresomes, amyloid, and lipofuscin accumulate across zones, aligning adrenal changes with systems-level proteome aging and vascular susceptibility. Key pathological correlates like ZR thinning, accumulation of aldosterone-producing cell clusters (APCCs), and higher prevalence of adrenal tumors underscore an age-biased remodeling of zonal identity and control hierarchies. Developmental and sex-dimorphic programs, including WNT/FRZB signaling and extracellular matrix remodeling, likely preconfigure later-life vulnerability. In this perspective , we synthesize these advances into a mechanistic model connecting centripetal differentiation, cholesterol trafficking, proteostasis collapse, inflammaging, and vascular aging to endocrine dysfunction and highlight biomarker strategies to index "adrenal age". We also outline near-term clinical deployment opportunities in older adults with adrenal incidentalomas or frailty using combined hormonal and plasma proteomic readouts, supported by human multi-organ proteomic evidence of proteostasis and vascular aging, aiming to restore cholesterol handling, reinforce proteostasis, and modulate senescence and niche signals.

Keywords: Adrenal aging, Zona reticularis, DHEA-S, LDLR, SULT2A1

1. Introduction

The adrenal cortex and medulla coordinate essential survival programs encompassing acute and chronic stress responses, blood pressure and electrolyte balance, glucose and lipid metabolism, immune modulation, and circadian entrainment [1-4]. Small in mass but systemic in reach, the gland's endocrine produces cortisol from the zona

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fasciculata (ZF), aldosterone from the zona glomerulosa (ZG), and adrenal androgens (primarily DHEA/DHEA-S) from the zona reticularis (ZR), all of which shape resilience to physiologic and environmental challenges across the life course [1-4].

With aging, clinical cohorts document a progressive decline in circulating DHEA/DHEA-S and, in many individuals, a reduction in aldosterone, whereas basal cortisol is on average preserved despite altered hypothalamic–pituitary–adrenal (HPA) dynamics [5-13]. Several datasets, however, show evening cortisol elevation and flattened diurnal slopes, and the prevalence of autonomous cortisol secretion increases with age [8, 9, 14-18]. These hormonal trajectories associate with frailty, sarcopenia, osteopenia, insulin resistance, immune dysfunction, and cognitive and affective changes [11-13, 19-23].

In line with the geroscience hypothesis, recent consensus frames "adrenal cortex senescence" or simply "adrenal aging" as a fundamental aging process that drives functional decline and contributes to age-related pathology [7, 24]. Endocrine drift, including ZR thinning, accumulation of aldosterone-producing cell clusters (APCCs), and increased prevalence of adrenal tumors/incidentalomas are accompanied by macro- and micro-structural changes [15-17, 25, 26]. Mechanistically, single-nucleus profiling of primate adrenals resolves cell states within cortical zones and reveals age-linked transcriptional, chromatin, and metabolic rewiring [27]. Cholesterol uptake machinery is implicated in functional perturbations in human adrenal cells as a rate-limiting constraint in aged steroidogenesis [27]. Proteostasis erosion, amyloid accumulation, and early vascular aging are identified in multi-organ human proteome atlases as transversal hallmarks that map onto adrenal vulnerabilities [28-30]. Developmental and sex-dimorphic programs (e.g., WNT/FRZB, extracellular matrix remodeling) suggest that the microscopic later-life susceptibility may emerge much earlier than overt aging [31-34].

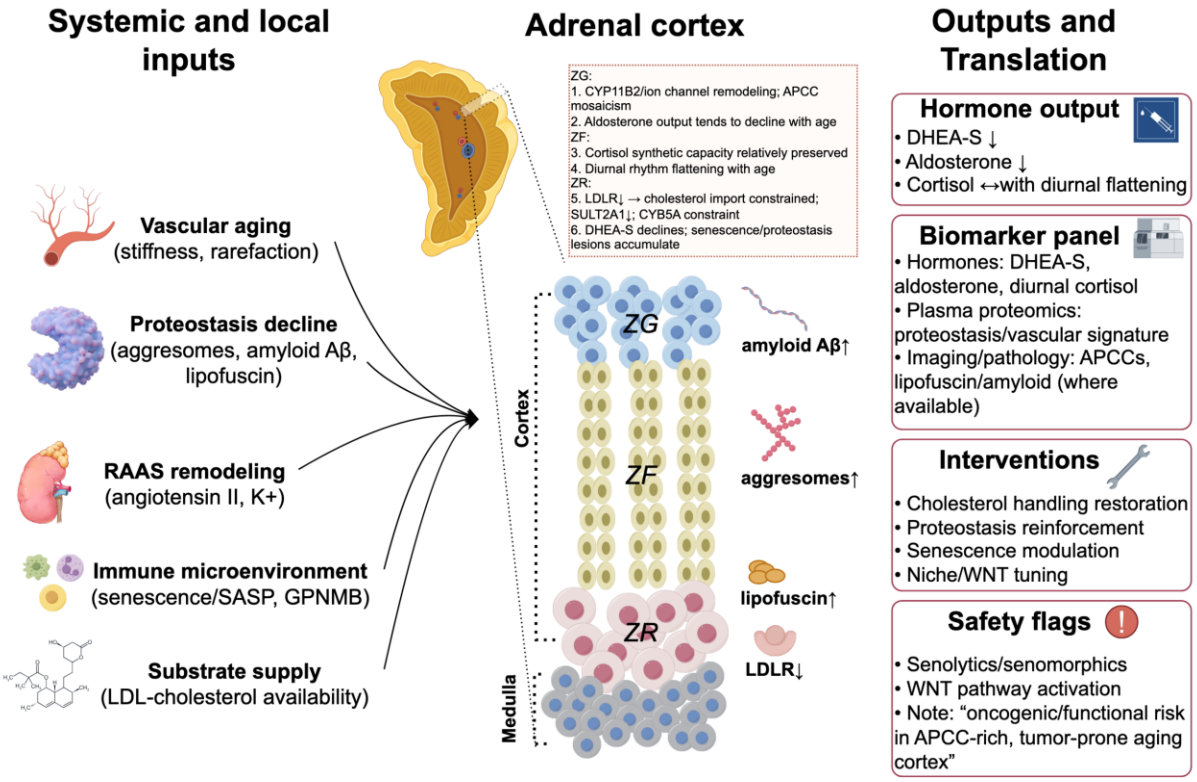

Figure 1. Overview of adrenal aging mechanisms and translation. Depicting zonal mechanisms, proteostasis lesions, vascular aging inputs, together with endocrine outputs, biomarker panel and intervention nodes with safety flags.

This perspective emphasizes mechanistic depth, integrating these threads into a framework for understanding and targeting adrenal aging featuring "methods snapshot" for ref. [27]: A cynomolgus monkey (Macaca fascicularis) adrenal atlas compared 7 young (4–6 years; ~human 18 years) and 8 aged (18–21 years; ~human 70 years) animals using single-nucleus transcriptomics and bulk RNA-seq, with histological

validation (p21, aggresomes, Aβ1-40, GPNMB, lipofuscin). Functional validation in human adrenal cells showed that LDLR knockdown reduced cholesterol uptake and selectively decreased DHEA-S secretion, linking substrate limitation to ZR failure.

We also note that most cohort studies include both sexes, with males exhibiting higher baseline DHEA/DHEA-S and greater absolute declines, while proportional declines are broadly similar. Menopausal transition further reduces and reshapes intracrine androgen context in women. In primate and human atlas data, sex was included but often underpowered for zone-level interaction tests. We thus flag this as a priority for future work.

Box 1. Glossary

- ZG: zona glomerulosa (aldosterone-producing)
- ZF: zona fasciculata (cortisol-producing)
- ZR: zona reticularis (androgen/DHEA-S-producing)
- APCC: aldosterone-producing cell cluster
- LDLR: low-density lipoprotein receptor
- SULT2A1: steroid sulfotransferase for DHEA sulfation
- CYB5A: cytochrome b5, enhances CYP17A1 17,20-lyase activity
-STAR/TSPO: cholesterol transport to the inner mitochondrial membrane
- Cholesterol trafficking: the balance of cholesterol acquisition (LDLR-mediated uptake), storage, mobilization, and mitochondrial delivery that limits steroid output
- (M)ACS: (mild) autonomous cortisol secretion

Adrenal aging is embedded within broader endocrine–immune networks: altered hypothalamic and pituitary control contributes to diurnal flattening, inflammaging and vascular aging constrain substrate and oxygen delivery, and adrenal endocrine drift feeds back on metabolic and immune tone. Figure 1 provides a graphical summary of zonal vulnerabilities, endocrine trajectories, proteostatic and vascular inputs, biomarker outputs, and intervention nodes. Figure 2 highlights zonal boundaries under these systemic influences.

2. Physiologic trajectories of adrenal hormones with age

DHEA/DHEA-S exhibits a pronounced decline from early adulthood through senescence, often exceeding a 70–80% reduction by the eighth decade [5, 6, 10, 12]. Beyond concentration, aging attenuates DHEA's diurnal rhythm and pulse amplitude [35-37]. DHEA-S is relatively diurnally stable as an albumin-bound reservoir that supports intracrine conversion by tissue sulfatases and sulfotransferases, regared as an important consideration for the functional consequences of declining levels, especially in post-menopausal women [38-41]. Aldosterone tends to decline with age on average, but the RAAS phenotype becomes complex, with suboptimal renin responsiveness and a presence of multiple, distinct areas within the adrenal glands that autonomously produce aldosterone [13, 42-44]. Histology reveals increased APCCs in older individuals, likely contributing to low-grade, age-associated aldosterone production independent of renin [25, 26, 45]. Cortisol output, on the other hand is broadly preserved at the population level, yet diurnal flattening and higher evening levels are common in older adults, and autonomous cortisol secretion, expecially its mild form (MACS) from adrenal incidentalomas becomes more prevalent [8, 9, 14-18]. Thus, "stable cortisol" masks heterogeneity, including a drift toward subtle hypercortisolism in a subset of elders.

These divergent endocrine trajectories imply zone-specific sensitivities. ZR androgenogenesis is particularly fragile, relying on intact cholesterol supply, efficient mitochondrial steroidogenesis through CYP17A1 with robust 17,20-lyase activity which is facilitated by its allosteric partner and electron donor CYB5A, and sulfation by SULT2A1 [1, 46-49]. ZG aldosterone production depends on substrate flux and mitochondrial CYP11B2 activity under RAAS control [1, 50]. ZF cortisol production is somehow buffered by redundancies, including substrate flexibility, large lipid reserves, and strong ACTH drive, potentially explaining its relative preservation despite altered diurnal regulation [1, 4, 50].

Clinically, these endocrine patterns map to common late-life presentations: (i) low DHEA-S and frailty/sarcopenia [51]; (ii) cardiovasular outcomes associated with even subclinical hyperaldosteronism [52]; and (iii) preserved yet flattened cortisol rhythms and age-biased ACS or MACS in incidentalomas [15]. These contexts motivate combined hormone monitoring with proteomic and imaging biomarkers to stage "adrenal age" and stratify risk.

Sex dimorphism also plays a role in adrenal physiology. Men demonstrate higher baseline DHEA/DHEA-S and experience larger absolute declines with age, whereas proportional declines are broadly similar between sexes. In women, menopause reduces ovarian steroid output and increases dependence on adrenal and intracrine androgen pathways, amplifying the functional impact of falling DHEA-S in late life. Aldosterone and cortisol trajectories show smaller sex effects at the population level, though body composition, RAAS tone, and HPA dynamics may contribute to inter-individual variability. Most datasets cited include both sexes, and where sex-stratified analyses are limited, we indicate this as a gap.

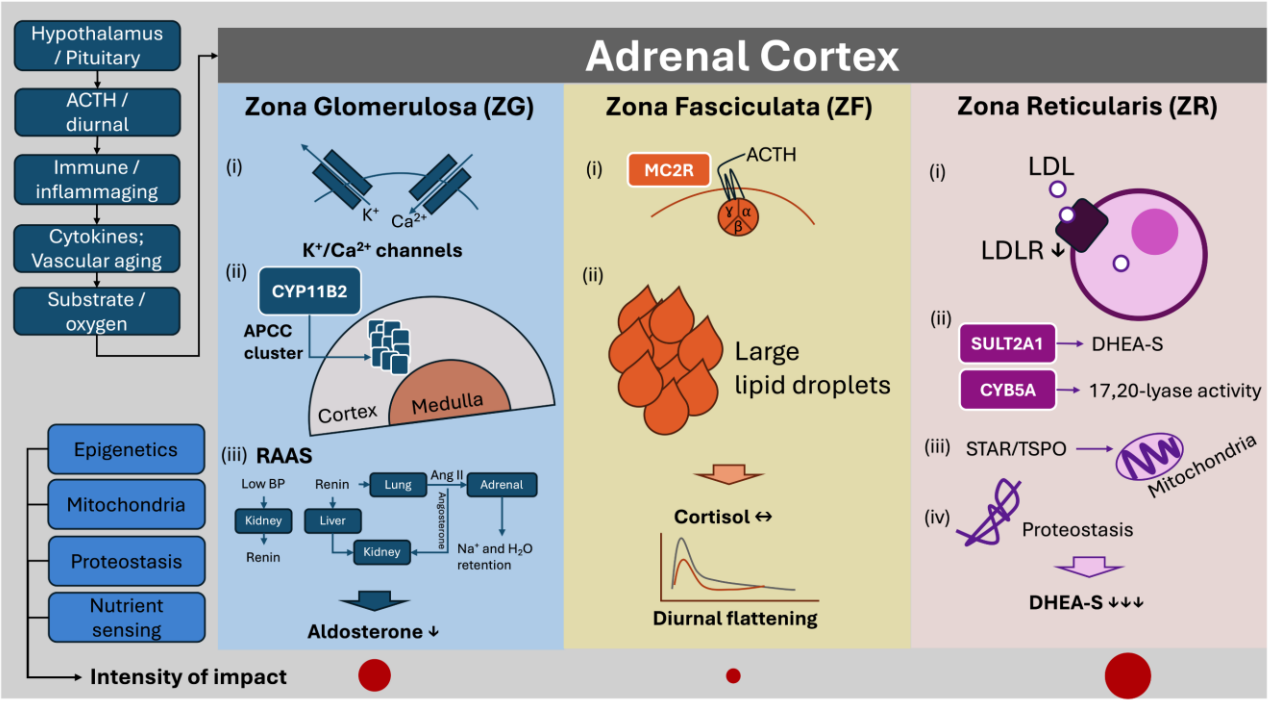

Figure 2. Functional boundaries and mechanisms by adrenal zonation. ZG (aldosterone) relies on CYP11B2, ion channel/RAAS control, and adequate cholesterol flux; age adds APCC mosaicism and reduced aldosterone in many individuals. ZF (cortisol) maintains synthetic capacity with strong ACTH drive, larger lipid reserves, and substrate flexibility but exhibits diurnal rhythm flattening. ZR (DHEA-S) is substrate-limited with LDLR downregulation, reduced SULT2A1 and CYB5A constraint, senescence, and proteostasis lesions; DHEA-S declines markedly.

3. Cellular and molecular hallmarks in aged primate adrenal glands

Single-nucleus transcriptomic and chromatin atlases of primate adrenal cortex has identified zone-specific aging signatures and candidate drivers [27]. ZR vulnerability is characterized by increased senescence and exhaustion programs with elevated cell-cycle inhibitors (e.g., p21), DNA damage responses, and SASP-like cytokine/chemokine signatures. Elevation of GPNMB and lysosomal markers indicates stress-adaptive remodeling [27, 53, 54] and downregulation of SULT2A1 and suppression of cholesterol uptake/processing genes are indicative of lipid handling and steroidogenesis derangements. A broad reduction of LDLR across outer cortical cell types constrains LDL-derived cholesterol import. In human adrenal cells, LDLR knockdown reduced cholesterol uptake and selectively lowered DHEA-S secretion, establishing substrate limitation as a driver of ZR failure [27]. Organelle stress signatures are characterized with activation of the ER UPR and mitochondrial dysfunction, with altered lipid droplet dynamics (SOAT1/ACAT1 balance; LIPE/HSL) that impair trafficking of cholesterol to the inner mitochondrial membrane via STAR and TSPO [27, 55-58]. ZG fragility features age-related decrements in CYP11B2 and RAAS pathway components that accompany inflammatory and vascular changes likely reducing oxygen and nutrient delivery critical for aldosterone biosynthesis. Remodeling of ion channels (e.g., KCNJ5, CACNA1D) that regulate membrane potential and calcium signaling may dampen aldosterone responsiveness [27, 50, 59, 60]. ZF however shows resilience by maintaining steroidogenic core machinery (STAR, CYP11A1, HSD3B2, CYP21A2, CYP11B1) better than ZR/ZG, possibly due to stronger ACTH/PKA signaling, larger neutral lipid reserves, and more robust proteostatic capacity. Nonetheless, age-associated changes in diurnal synchronization and feedback sensitivity are evident and may contribute to the rise in mild or overt autonomous cortisol secretion [1, 4, 18, 27]. These changes align with core aging hallmarks, namely mitochondrial dysfunction at the cholesterol import and electron transfer nexus (STAR/TSPO/CYB5A), epigenetic and chromatin remodeling shaping steroidogenic identity, and nutrient-sensing/AMPK–mTOR effects on lipid droplet dynamics, autophagy, and proteostasis.

Proteostatic lesions, including aggresomes, amyloid-like aggregates, and lipofuscin accumulate with age. Lipofuscin is particularly enriched in ZR, consistent with high oxidative load and turnover. These pathologies imply

insufficient autophagy–lysosome and proteasome function and align with multi-organ observations of transcriptome–proteome decoupling and amyloid accumulation [28-30, 61-65]. In steroidogenic cells, misfolded cytochromes and mitochondrial transporters are liabilities because biosynthetic flux hinges on precise enzyme stoichiometry, redox coupling, and membrane integrity [1, 55, 62]. These adrenal lesions align with human multi-tissue proteomic evidence for age-associated proteostasis decline and amyloid accumulation, and with an early-aging trajectory of blood vessels accompanied by a plasma proteomic signature [28]. Given the adrenal's dense vascularization, early vascular aging may compound substrate and oxygen delivery constraints in ZG/ZR. Collectively, proteostasis erosion (aggresomes, amyloid, lipofuscin) intersects with mitochondrial stress and impaired autophagy, consistent with hallmark pathways, while human proteomics identifies a plasma signature tracking proteostasis and vascular aging, offering a feasible adjunct for "adrenal age" staging [28].

Other changes includes inflammaging that features increase in inflammatory signaling, antigen presentation, and leukocyte recruitment signatures. Endothelial and perivascular cell states shift toward pro-inflammatory, pro-fibrotic phenotypes, altering nutrient exchange and paracrine cues crucial for cortical renewal [27-30, 66-68]. As the cortex renews via centripetal differentiation from capsular/peripheral progenitors under WNT/SHH and zona-specific cues, aging appears to blunt progenitor output and disrupt WNT gradients, with consequences for maintaining ZR identity and replenishing steroidogenic cells [27, 31-34, 69]. Extrapolated from findings in primates, human pathology correlates aligns with omic profile, featuring ZR thickness diminishes with age, APCCs accumulate in ZG, and adrenal adenomas/incidentalomas become more prevalent [15-17, 25, 26]. These features likely reflect age-related niche remodeling and clonal selection under altered RAAS and inflammatory tone, dovetailing with transcriptomic evidence of impaired differentiation and lipid handling [15-17, 25-27, 42-45].

Together, the data support a model in which cholesterol import bottlenecks (LDLR and potentially SR-BI/SCARB1), organelle stress, and proteostasis failure converge on ZR steroidogenesis, while vascular and inflammatory remodeling further constrain ZG and ZR more than ZF [1, 20-22, 27-30, 42, 46, 61-68]. Micro-nodular and clonal changes in ZF help explain rising autonomous cortisol secretion despite preserved average capacity [15-18] (Table 1).

Table 1. Circulating proteomic candidates relevant to adrenal aging: directionality, source tissues, and potential clinical value [28].

Protein alteration with age	Dominant source(s)	Clinical value and notes
GDF15 ↑	Multiple (muscle, liver, endothelium; stress-responsive)	Robust aging marker; mitochondrial/ISR link; frailty and cardiometabolic risk stratification; adjunct to "adrenal age" panel
Clusterin ↑	Liver, brain, secretory tissues; chaperone	Proteostasis/amyloid handling; aligns with adrenal proteostatic lesions; proxy for proteostasis load
GAS6 ↑	Vascular cells, immune/stromal	Candidate senoprotein; vascular/systemic aging; links to vascular inputs that constrain adrenal zones; may flag APCC-prone milieu
VCAM1 ↑	Endothelium	Vascular inflammation/early vascular aging; substrate delivery constraint proxy; integrates with adrenal perfusion dependence
IGFBP7 ↑	Endothelium, VSMC, kidney	Vascular stiffness/fibrosis marker; cardiometabolic risk; adds vascular component to adrenal age
SERPINA3 ↑	Liver (acute phase)	Proteostasis and amyloid-associated acute-phase response; complements CLU for proteostasis axis
B2M ↑	Broad (immune/renal handling)	General aging/inflammation; caution with renal function; captures systemic proteostasis/inflammaging
LCN2 ↑	Neutrophils, liver	Inflammation/stress marker; relates to adrenal-immune crosstalk; caution for renal confounding
APOE (total) ↑ **(Context-dependent)**	Liver, CNS	Amyloid and lipid handling; may track proteostasis/amyloid environment
MMP9 or TIMP1 ↑	Vascular/immune; liver (TIMP1)	ECM remodeling/vascular aging; relevant to ZG niche and APCC-associated remodeling

4. Adrenal aging in the context of system proteomics and vascular aging

Recent human proteome aging atlases also shed light on cross-tissue features relevant to the adrenal gland [28-30, 61, 64, 65]. Aging tissues show growing burdens of insoluble proteins, amyloid-like assemblies, and decoupling between mRNA and protein abundances. Chaperone networks, autophagy–lysosome pathways, and mitochondrial quality control progressively falter. Because steroidogenesis is intensely proteome-dependent, requiring rapid turnover of P450 enzymes, redox partners, and transporters, proteostasis decline disproportionately impacts adrenal function [28-30, 61-65].

Amongst all tissues, the vasculature exhibits accelerated proteomic aging, characterized with extracellular matrix crosslinking and stiffening, basement membrane thickening, endothelial dysfunction, and pro-thromboinflammatory remodeling. For the adrenal gland, which relies on a rich sinusoidal blood supply and cortico-medullary portal circulation, vascular aging can restrict cholesterol delivery and oxygen availability (critical for mitochondrial P450 monooxygenases), impede hormonal egress, and desseminate inflammatory signals that suppress steroidogenesis via NF-κB and interferon signaling [1, 4, 28-30, 50, 66-68]. Thus, plasma proteins reflecting senescent cell burden and vascular damage rise with age and correlate with organ-specific proteomic "clocks." Such signatures could serve as indirect sensors of adrenal biological age when combined with endocrine readouts [20-22, 28-30, 65].

Also, the rise in APCCs and age-associated autonomous cortisol secretion fits a broader theme of age-biased clonal and micro-nodular remodeling in endocrine tissues under vascular and inflammatory stress [15-18, 25, 26, 66-68]. This systems perspective situates adrenal aging within a network: failing proteostasis and vascular aging act as upstream constraints on steroidogenic performance, while adrenal hormone decline feeds back onto vascular, immune, and metabolic aging trajectories [20-22, 28-30, 66-68].

5. Developmental and sex-dimorphic programs: insights for aging mechanisms

Despite lacking ZR, mouse adrenal time-course transcriptomics across postnatal development highlight sex-dimorphic trajectories that plausibly shape later-life vulnerability. Sex differences in steroidogenic and lipid metabolism genes widen across adolescence, influenced by intrinsic (including Y-linked) programs and, later, by gonadal hormones. Expression of cholesterol processing genes (LDLR, SCARB1, SOAT1, LIPE) and steroidogenic enzymes shows distinct male–female patterns that could precondition zone-specific reserves and stress responses [1, 31, 32, 34].

Weighted gene co-expression analyses implicate WNT signaling as a key organizer of cortical zonation. The WNT antagonist FRZB shows dynamic, sex- and age-dependent expression, localizing to inner cortical regions supportive of ZR identity. Declining FRZB and altered WNT tone with age may destabilize ZR fate and centripetal differentiation, reducing androgenogenic output. Extracellular matrix (ECM) remodeling featuring progressive changes in collagen and matrix transcripts during maturation suggests dynamic matrix tuning. With aging, maladaptive ECM stiffening and basement membrane changes that could be amplified by vascular aging may impair progenitor migration, nutrient diffusion, and paracrine signaling, compounding functional decline [31, 32, 34, 66-68]. Intracrine dependence on DHEA/DHEAS for sex steroid production, especially in post-menopausal women, may amplify the clinical visibility of these sex-dimorphic developmental programs as ZR output declines [38-41].

6. Mechanistic integration: from cholesterol trafficking to proteostasis and inflammaging

Adrenal steroidogenesis is a logistics problem: trafficking cholesterol to the right place, at the right time, with enzyme machinery ready to convert it into zone-specific hormones. Aging disrupts this logistics chain at multiple levels [1, 27-30, 46, 55-58, 61-68]. Cholesterol supply depends on receptor-mediated uptake (LDLR for LDL; SR-BI/SCARB1 for HDL), de novo synthesis (SREBP2/HMGCR axis), and mobilization from cholesteryl ester stores (SOAT1/ACAT1 balance and LIPE). Primate cortex shows a broad downshift in LDLR across outer cortical cell types, and LDLR loss selectively throttles DHEA-S secretion, implying a particular dependence of ZR on LDL-derived cholesterol. SR-BI-mediated HDL uptake may partly compensate but is limited by vascular HDL functionality and SR-BI expression [1, 27, 42, 46, 50]. Intracellular trafficking requires STAR and TSPO to deliver cholesterol to the inner mitochondrial membrane for CYP11A1 cleavage. ER–mitochondria contacts and cytoskeletal transport orchestrate the flux. Aging-associated ER stress and mitochondrial dysfunction impede this orchestration, lowering effective substrate delivery even when cellular cholesterol pools are adequate [1, 27, 55-58, 61, 62].

Steroidogenic P450s and redox partners generate ROS during catalysis. With age, antioxidant defenses and mitochondrial proteases may be insufficient to prevent oxidative damage and misfolding. Accumulated aggregates, lipofuscin, and amyloid-like deposits burden

autophagy–lysosome and proteasome pathways, reducing functional enzyme availability. This proteostasis collapse is especially detrimental in ZR, where CYP17A1/17,20-lyase activity hinges on tight coordination with CYB5A and PKA/ERK signaling [1, 47-49, 55, 61-65]. Moreover, age-related increases in pro-inflammatory cytokines and leukocyte adhesion molecules in adrenal stroma and endothelium suppress steroidogenic gene expression via NF-κB and STAT signaling, inhibit STAR, and alter calcium dynamics. Endothelial dysfunction reduces oxygen and nutrient delivery and may diminish SR-BI–mediated HDL flux [1, 20-22, 27-30, 50, 66-68].

The adrenal cortex renews from capsular progenitors under WNT/β-catenin and SHH guidance, with zona-specific maintenance programs. With age, progenitor output and gradient fidelity decline with WNT antagonists (e.g., FRZB) and ECM changes destabilizing inner cortical zoning. ZR is particularly sensitive to modest perturbations in these fate-maintenance signals [1, 27, 31-34, 69]. APCCs likely emerge as adaptive/maladaptive endpoints under chronic RAAS/inflammatory stress and vascular aging, shifting aldosterone control from systemic feedback to local autonomy. In ZF, micro-nodular clonal expansions and proteostasis stress offer a mechanistic basis for the age-related rise in autonomous cortisol secretion despite preserved average capacity [15-18, 25, 26, 42, 45, 59, 60, 66-68]. ZF resilience arises from stronger ACTH drive, larger lipid droplets offering substrate buffering, potentially higher baseline SR-BI expression, and a proteostasis environment that, while stressed, remains above the failure threshold. ZF enzymes may be less sensitive to reductions in CYB5A or LDLR than ZR machinery [1, 4, 46, 50].

In all, this integrated model explains the selective fall of DHEA-S and aldosterone with age and the parallel emergence of hormone autonomy, implicating cholesterol economics and proteostasis as central limiting processes modulated by vascular and inflammatory milieu and impaired differentiation [1, 4, 15-17, 20-22, 25-30, 42, 46, 50, 61-69].

7. Biomarkers and biological age of the adrenal gland

DHEA-S is the most practical plasma biomarker of adrenal aging, reflecting ZR output with minimal diurnal variation. DHEA rhythm attenuation may add information in research settings [5, 6, 35-37]. Aldosterone and renin (plasma renin activity/concentration) index ZG function but are sensitive to posture, salt, medications, and renal function. The aldosterone–renin ratio can detect drift toward aldosterone autonomy as APCCs emerge [13, 25, 26, 42-45]. Cortisol (AM peak, diurnal slope) reveals HPA feedback changes. Low-dose dexamethasone tests and steroid profiling can detect mild or overt ACS in older adults with adrenal nodularity [4, 15-18].

SULT2A1, LDLR, SR-BI, STAR, CYP17A1/CYB5A expression provide windows into mechanistic status of ZR. Functional assays of cholesterol trafficking and mitochondrial steroidogenic capacity can serve as intermediate biomarkers [1, 27, 46, 55-58]. A more clinically friendly test assy is combining endocrine metrics with plasma proteins linked to senescence burden, vascular aging, and proteostasis that may index the adrenal's biological age indirectly. A composite "adrenal age" score could weight age- and sex-normalized DHEA-S percentile, RAAS-adjusted aldosterone and renin, proteomic senescence/proteostasis markers, and clinical covariates (blood pressure, lipids, glycemia, renal function) [20-22, 28-30, 65].

From intracrine point of veiw, tissue sulfatase/sulfotransferase activity modulates the functional impact of a given DHEA-S concentration and in research settings, assays for these enzymes could refine biological age estimates on the adrenal–androgen axis, particularly in post-menopausal women [38-41]. Alternatively, dynamic tests like ACTH stimulation, angiotensin II challenge, posture testing, and low-dose dexamethasone suppression can reveal reserve capacity, signaling integrity, and emerging autonomy and their age-related attenuation patterns can refine biological age estimates [1, 4, 15-17, 50].

8. Therapeutic opportunities and testable strategies

Any intervention to rejuvenate adrenal function must balance cholesterol availability, proteostasis load, inflammatory tone, adverse events and oncogenic risk in a tissue prone to hyperplasia and neoplasia under chronic trophic stimulation. Combination strategies are likely required [1, 20-22, 24, 61-68].

Receptor-mediated uptake by enhancing LDLR or SR-BI function in adrenal cortex could relieve substrate bottlenecks. Systemic LDLR upregulation (e.g., PCSK9 inhibition) reduces circulating LDL-C but whether net adrenal cholesterol delivery improves is uncertain and may vary by zone. Elevating HDL-C and HDL functionality (e.g., CETP inhibition) could augment SR-BI–mediated uptake. Adrenal-targeted approaches to preserve SR-BI under oxidative stress warrant exploration [1, 42, 46, 50, 66-68]. Intracellular mobilization and trafficking may also be targeted by modulating SOAT1 to balance storage and availability, enhancing LIPE-mediated hydrolysis of cholesteryl esters, and reinforcing STAR/TSPO transport, all converging to increase mitochondrial substrate delivery [1, 55-58] . Of note, augmenting cAMP/PKA must be balanced against hypercortisolism risk [1, 4, 50]. Alternatively, boosting de

novo cholesterol synthesis via SREBP2 risks systemic adverse effects and organ-targeted delivery may be necessary [1, 42, 46].

Another approach is reinforcement of proteostasis and organelle quality control. Autophagy–lysosome induction (e.g., TFEB/TFE3 activation; cautious mTORC1 modulation) may clear aggregates and damaged organelles, with attention to dose and schedule to avoid impairing steroidogenesis [61, 62, 70]. Agents that stabilize mitochondrial membranes and reduce ROS (e.g., mitochondria-targeted antioxidants) may preserve P450 function while adrenal-specific testing is needed [61, 62, 71, 72]. Selective enhancement of chaperone capacity may also fit in but indiscriminate HSP90 inhibition is counterproductive for steroidogenic complexes [1, 61].

Senolytics can clear senescent cells but risk collateral loss of supportive stromal compartments whereas senomorphics (e.g., JAK/STAT or p38 pathway modulators, metformin) may suppress SASP and restore steroidogenic signaling with fewer risks [20-22, 73]. Endothelial-protective measures (ACE inhibitors/ARBs, SGLT2 inhibitors, exercise) may improve substrate delivery and reduce inflammatory suppression of steroidogenesis [66-68]. Fine-tuning WNT signaling to stabilize ZR identity and centripetal differentiation is attractive (e.g., FRZB mimetics or RSPO modulation), but systemic manipulation carries tumorigenic risk. Local delivery or biomaterials that restore ECM elasticity and niche factors could support progenitor function with less systemic exposure [31-34, 69]. In addition, sleep regularity, light exposure, and stress management may normalize ACTH rhythms, preserving ZF health and whether this secondarily benefits ZR and ZG through shared trafficking machinery is testable [2, 4, 8, 9].

Notablly, DHEA supplementation has been most clinically accesible but debatable. Trials show mixed effects. While some show improvements in vascular surrogate markers, others argue that hard cardiovascular or mortality benefits are unproven. Given the intracrine conversion and sex-specific contexts, targeted use may be reasonable in select hypoadrenal or deficient states, but for aging per se, upstream strategies (restoring cholesterol handling, proteostasis, and microvascular health) may address root causes more effectively. Safety monitoring for androgenic/estrogenic effects remains essential [12, 19, 38, 39].

To address translational hurdle, suitable preclinical models is at need. Human adrenal cell systems and iPSC-derived adrenal organoids that ideally incorporating endothelial and immune components can screen LDLR/SR-BI restoration, proteostasis enhancers, and senescence modulators. Nonhuman primate studies, given closer ZR biology, are crucial for translational validation and endocrine safety. In vivo tests of endothelial rejuvenation or anti-inflammatory strategies could probe causality between vascular aging and zone-specific function [27-31, 69, 74, 75].

9. Outstanding questions and experimental priorities

(1) Can we derive and validate an "adrenal age" composite biomarker that integrates endocrine outputs (DHEA-S, RAAS-adjusted aldosterone/renin), dynamic testing, and plasma proteomics, and does it predict morbidity and therapeutic responsiveness beyond chronological age? [15-17, 25, 26, 28-30, 65].

(2) What are the causal links between vascular aging, inflammaging, and zone-specific function in vivo? Do endothelial-targeted rejuvenation strategies restore cholesterol and oxygen delivery sufficiently to rescue ZR/ZG output? [20-22, 28-30, 66-68].

(3) What is the causal sequence linking RAAS dysregulation, APCC emergence, and aldosterone decline versus autonomy with age, and can micro-aldosteronism be reversed by vascular or anti-inflammatory interventions? [13, 25, 26, 42-45, 66-68].

(4) How plastic is the adult ZR, and to what extent can WNT/FRZB or SHH pathway tuning reestablish ZR identity and androgenogenic capacity without neoplastic risk? [31-34, 69].

(5) Are proteostasis defects in steroidogenic cells reversible at clinically tolerable doses? Which nodes (autophagy, mitochondrial proteases, chaperones) deliver the best benefit–risk profile? [61-63, 70-72].

(6) What are the identities and impacts of senescent cell populations within adrenal cortex (ZR steroidocytes, capsular progenitors, endothelial/perivascular cells), and can selective clearance or SASP suppression restore steroidogenesis safely? [20-22, 27, 53, 54, 73].

(7) How do sex differences in developmental programming intersect with aging trajectories and therapeutic windows? Should interventions be sex-tailored? [31-34, 38-41].

(8) To what degree does HPA axis remodeling with age—altered ACTH pulsatility and feedback—secondarily influence ZR/ZG decline, and can central interventions meaningfully ameliorate peripheral cortical aging? [2, 4, 8, 9, 18].

(9) Can intracrine capacity (sulfatase/sulfotransferase activity) be quantified noninvasively to contextualize declining DHEA-S and predict tissue-level androgen/estrogen availability? [38-41].

10. Translational outlook: patient groups, biomarkers, and timelines

In effort to combine current tech and prospective reaserch directions, we propose a translational outlook. For Older

adults with adrenal incidentalomas or (M)ACS, combine diurnal salivary/serum cortisol profiling, DHEA-S, and targeted imaging; consider APCC-linked genetics where available; and monitor cardiometabolic endpoints. In case of frailty/sarcopenia with low DHEA-S, measure periodic DHEA-S with functional metrics (e.g., grip strength, gait speed), consider intracrine tissue context in women, and evaluate adrenal-centric plasma proteomic panels. As for age-associated dysaldosteronism, integrate renin/aldosterone with volume status and blood pressure, and contextualize APCC burden.

We also prospect the deployment timelines. Near-term (now to ~2 years) includes standardized diurnal cortisol and DHEA-S; integrate plasma proteomic signatures reflecting proteostasis/vascular aging as adjunct "adrenal age" indices; pathology-based APCC quantification in surgical specimens; and MRI/CT radiomics exploration in incidentalomas. Mid-term (2–5 years) may encompass trials of cholesterol-handling restoration, proteostasis reinforcement strategies, and senescence-modulating regimens with adrenal-specific endpoints and safety gates. All those prospective mandate high quality trials as current evendence on DHEA/DHEA-S supplementation has shown mixed functional benefits in older adults and post-menopausal women [76, 77] and ACS/incidentaloma cohorts demonstrate cardiometabolic risk modification with tailored management. Prospective adrenal-centric trials using multi-omic biomarker panels remain a gap and priority.

11. Safety, ethics, and trial design considerations

Lastly, interventions that modulate senescence or WNT carry oncogenic and off-target risks, particularly in an organ with age-increasing incidentalomas and APCCs. We prioritize (i) pathway-adjacent strategies with favorable safety, (ii) staged evaluation in human adrenal cell models and ex vivo tissues, (iii) adaptive trial designs with endocrine and oncologic stopping rules, and (iv) vigilant imaging and hormonal surveillance.

12. Conclusions

Adrenal aging is a regionally focused failure of a high-throughput biosynthetic machine under mounting constraints. ZR and ZG are disproportionately compromised by cholesterol substrate scarcity, organelle stress, and proteostasis decline, all amplified by vascular aging and inflammaging and compounded by drift in differentiation cues [1, 4, 15-17, 20-22, 25-30, 42, 46, 50, 61-69]. Human pathology corroborates omic evidence that age remodels zonal identity and control hierarchies, predisposing to mosaic hormone autonomy amid global androgen and mineralocorticoid decline [15-17, 25, 26]. ZF cortisol output is comparatively preserved, reflecting distinct reserve capacities and trophic support, yet heterogeneity emerges with diurnal flattening and rising autonomous cortisol secretion [8, 9, 14-18]. This mechanistic view yields actionable hypotheses: improve cholesterol flux, upgrade proteostasis and mitochondrial quality control, temper senescence-driven inflammation, and stabilize zonal identity and vascular–stromal support [1, 20-22, 24, 27-34, 61-72]. Strategic biomarker development will be essential to measure adrenal biological age and to guide trials [15-17, 25, 26, 28-30, 65]. With attention to zone specificity, intracrine context, and systemic safety, the adrenal gland may prove to be both a readout and a lever for improving healthspan [7, 24].

Conflict of interest

None.

Authors' contributions

Conceptualization: CF, GD; Methodology: CF, TG; Validation: GD; Investigation: YX, TG; Original Draft: CF, YX.

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