Genes & Immunity
https://doi.org/10.1038/s41435-020-0096-6

REVIEW ARTICLE

Extra-adrenal glucocorticoid biosynthesis: implications for autoimmune and inflammatory disorders

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Received: 5 December 2019 / Revised: 5 March 2020 / Accepted: 9 March 2020
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Abstract

Glucocorticoid synthesis is a complex, multistep process that starts with cholesterol being delivered to the inner membrane of mitochondria by StAR and StAR-related proteins. Here its side chain is cleaved by CYP11A1 producing pregnenolone. Pregnenolone is converted to cortisol by the enzymes 3-βHSD, CYP17A1, CYP21A2, and CYP11B1. Glucocorticoids play a critical role in the regulation of the immune system and exert their action through the glucocorticoid receptor (GR). Although corticosteroids are primarily produced in the adrenal gland, they can also be produced in a number of extra-adrenal tissue including the immune system, skin, brain, and intestine. Glucocorticoid production is regulated by ACTH, CRH, and cytokines such as IL-1, IL-6, and TNFα. The bioavailability of cortisol is also dependent on its interconversion to cortisone, which is inactive, by 11βHSD1/2. Local and systemic glucocorticoid biosynthesis can be stimulated by ultraviolet B, explaining its immunosuppressive activity. In this review, we want to emphasize that dysregulation of extra-adrenal glucocorticoid production can play a key role in a variety of autoimmune diseases including multiple sclerosis (MS), lupus erythematosus (LE), rheumatoid arthritis (RA), and skin inflammatory disorders such as psoriasis and atopic dermatitis (AD). Further research on local glucocorticoid production and its bioavailability may open doors into new therapies for autoimmune diseases.

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Introduction

Glucocorticoids, autoimmune and inflammatory disorders in a nutshell

The biosynthesis of steroid hormones starts from cholesterol, which in turn is derived from a number of sources including de novo synthesis, lipoprotein-derived cholesteryl esters, and cholesteryl esters stored in lipid droplets [1–3]. Hormonal regulation of steroid biosynthesis occurs within minutes (acute) to hours (chronic) and is primarily mediated by cAMP signaling [3–7]. Steroid hormones are largely synthesized in steroidogenic cells of the adrenal, ovary, testis, placenta, and brain; however, they are also produced in a number of extra-adrenal and -gonadal tissues. Glucocorticoids play critical roles in a wide variety of physiological processes, including regulation of various developmental and homeostatic pathways, and display several immune functions [3, 8]. Their release and production are regulated primarily by ACTH (adrenocorticotropic hormone) and indirectly by CRH (corticotropin releasing hormone) [1].

Published online: 23 March 2020

Autoimmune disease and skin inflammatory disorders represent a significant clinical problem affecting large segments of the population and the quality of life of affected patients, and impose a significant cost to the economy, and the health care system in particular. While there are different factors underlying the etiology of multiple sclerosis (MS), lupus erythematosus (LE), rheumatoid arthritis (RA), and skin inflammatory disorders such as psoriasis and atopic dermatitis (AD), they are linked by one element, the diseases are a consequence of a dysfunctional/hyperactive immune system. Glucocorticoids are used worldwide to treat autoimmune disease and inflammatory disorders. Since the skin and systemic immune cells can produce glucocorticoids as well as their hormonal regulators, we are exploring the hypothesis that autoimmune and inflammatory diseases develop and progress due to a malfunction of local glucocorticosteroid signaling and that their regulators play a role in the development and progression of autoimmune and inflammatory diseases.

Glucocorticoid synthesis

Molecular and biochemical principles of glucocorticoid biosynthesis

Cholesterol transport into the inner mitochondria

Glucocorticoid synthesis is a complex and multiregulated process that predominately takes place in the adrenal cortex. A schematic of this process is shown in Fig. 1. It starts with the mobilization and delivery of cholesterol from the outer to the inner mitochondrial membrane, a process that is mediated by the steroidogenic acute regulatory protein (StAR; also called STARD1) and also involves StAR-related lipid transfer domain containing 3 (STARD3), also known as metastatic lymph node protein, clone 64 or MLN64), and possibly the translocator protein (TSPO; known previously as peripheral benzodiazepine receptor, PBR).

The mitochondrial StAR protein plays an indispensable role in the regulation of steroid hormone biosynthesis, i.e., the transfer of cholesterol from the outer mitochondrial membrane to the inner membrane site where CYP11A1 converts it to pregnenolone [3, 4, 9, 10]. Regulation of the expression, activation, and/or degradation of StAR is influenced by cAMP/protein kinase A (PKA), protein kinase C (PKC), as well as a host of other signaling pathways [3, 4, 11–16]. Therefore, control of StAR expression involves the interaction of a diversity of hormones and signaling pathways that coordinate the cooperation and interaction of various transcriptional regulators, as well as a number of post-transcriptional events that govern mRNA and protein expression [2, 17, 18]. Regardless of the regulatory events, there is a tight correlation between the synthesis of steroids and the synthesis of StAR mRNA/protein in a variety of classical and non-classical steroidogenic tissues [3, 19]. StAR has been implicated in virtually all cholesterol- and/or steroid led processes that involve endocrine, autocrine, and paracrine events [3, 20–24].

STARD3 has significant homology with the StAR protein and belongs to the START domain subfamily of 15 proteins (STARD1-STARD15), and it is localized in late endosomes and lysosomes [25, 26]. The START domain proteins, STARD1 and STARD3-6 bind a variety of sterols, including cholesterol, 25-hydroxycholesterol, and oxysterols, and are involved in intracellular cholesterol trafficking, lipid metabolism, and signal transduction [27, 28]. There is increasing evidence that STARD3 plays an important role in the intracellular transport of cholesterol from endosomes to the mitochondria for sustaining steroidogenesis. STARD3 is ubiquitously expressed in tissues suggesting a role in a variety of sterol mediated regulatory processes. In tissues such as the human placenta that do not express StAR, cholesterol delivery to CYP11A1 is mediated by STARD3 [25, 29]. It is assumed that STARD3 may deliver cholesterol to the mitochondria through transient interactions between the START domain and the outer mitochondrial membrane, as occurs for the StAR protein [30]. Taken together, STARD3, by transporting cholesterol from late endosomes and/or lysosomes to the mitochondria, influences steroidogenesis.

Translocator protein (TSPO) is ubiquitously expressed in tissues, most abundantly in mitochondria of steroid producing cells. Several studies reported that it plays a key role in controlling steroid biosynthesis [31–35]. TSPO binds cholesterol with high affinity and has been implicated in the transport of cholesterol to the inner mitochondrial membrane. Aberrant expression of TSPO has been linked to various complications and multiple diseases, including neurodegeneration, brain injury, ischemia reperfusion injury, and cancers [36–40]. The association of upregulation of TSPO expression with neuronal damage and inflammation makes it an important biomarker for neurodegenerative diseases. However, serum pregnenolone levels and pregnenolone synthesis by isolated mitochondria were found to be unaltered in global TSPO knockout mice, which cast doubts over an essential role of TSPO in steroidogenesis [41].

Glucocorticoid biosynthesis

The biochemistry of glucocorticoid biosynthesis is well established. This biochemical pathway is shown in Fig. 1. In the inner mitochondrial membrane, CYP11A1 converts cholesterol to pregnenolone, a precursor of all steroids [1, 42]. CYP11A1 can also convert 7-dehydrocholesterol to

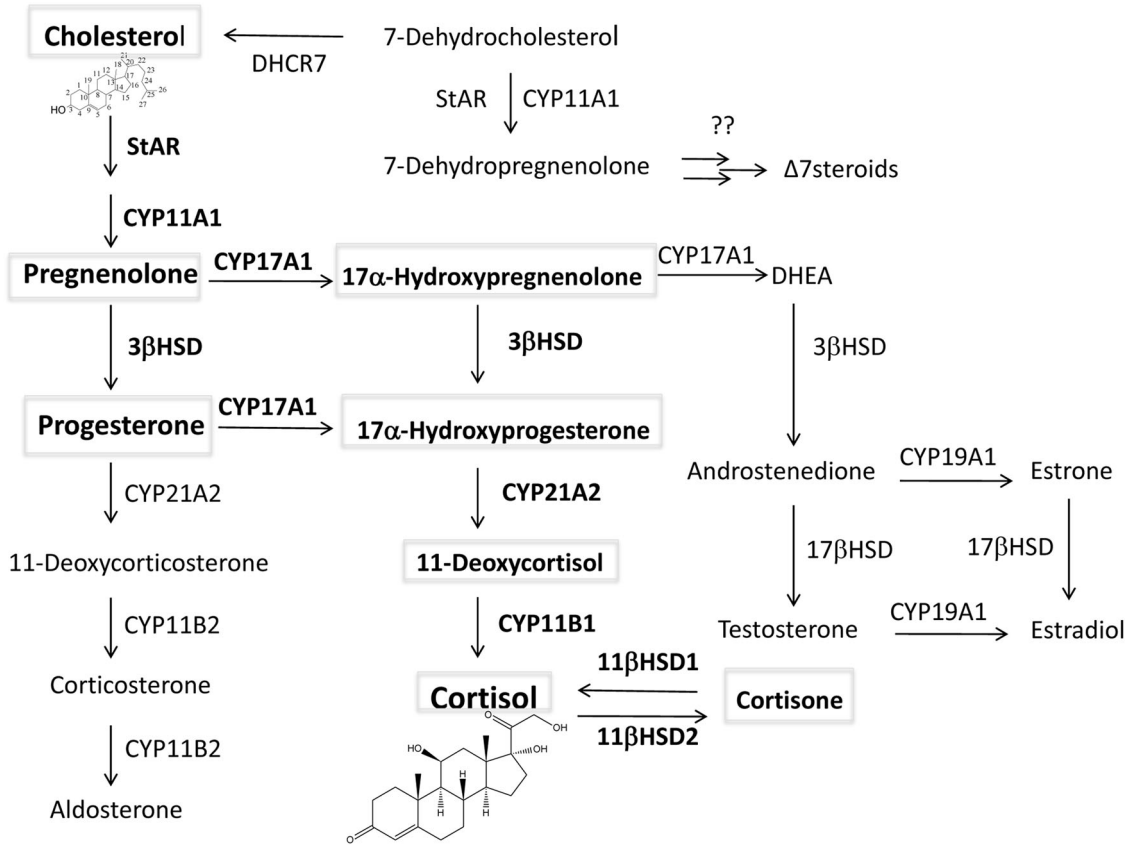

Fig. 1 The biochemical pathway of steroidogenesis. Glucocorticoid synthesis is in bold. DHCR7: 7-delta reductase; 3βHSD: 3β-hydroxysteroid dehydrogenase.

7-dehydropregnenolone and hydroxylates vitamin D, ergosterol and lumisterol to their corresponding hydroxyderivatives, with some side chain cleavage also occurring with lumisterol [43–49]. Pregnenolone can either serve as substrate for 3β-hydroxysteroid dehydrogenase (3-βHSD), which converts it to progesterone or be converted to 17α-hydroxypregnenolone by the enzyme CYP17A1 [50, 51]. The former reaction involves the oxidation of the 3β-hydroxyl group to a ketone group and the movement of the double bond from C5 to C4 through an isomerization reaction [1]. Progesterone is then converted to corticosterone by the actions of CYP21A2 and CYP11B1, while these same enzymes convert 17α-hydroxyprogesterone to cortisol [1, 52]. 7-Dehydropregnenolone can be metabolized by steroidogenic enzymes to the corresponding Δ7steroids (androgens and estrogens) as demonstrated experimentally [47, 53, 54], and predicted from the steroid profile in Smith–Lemli–Opitz syndrome [55–58]. However, Δ7 glucocorticoids cannot be produced from 7-dehydropregnenolone [53]. Since cortisol is the predominant glucocorticoid in humans, the manuscript will focus on cortisol.

Peripheral glucocorticoid bioavailability is also dependent on the two enzymes, 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) and 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) [59, 60]. 11βHSD1 can act as both an activator of glucocorticoids by reducing cortisone to cortisol and as an inactivator by oxidizing cortisol to cortisone, depending on the NADPH and NADP levels [1, 59]. 11βHSD2 on the other hand acts only as an oxidase, converting the hydroxy group at C11 of cortisol to a ketone, generating cortisone [1, 59, 60]. One of the roles of 11βHSD2 is to prevent nonselective binding of cortisol to the mineralocorticoid receptor, thus enabling aldosterone to be the dominant mineralocorticoid [59].

Hypothalamic-pituitary adrenal (HPA) axis: CRH and ACTH

Overview of hypothalamic pituitary adrenal (HPA) axis

The HPA axis is the main regulator of the stress response as well as for systemic glucocorticoid production [61, 62]. CRH is the key regulator of the HPA and is produced in the paraventricular nucleus of the hypothalamus [63]. Under

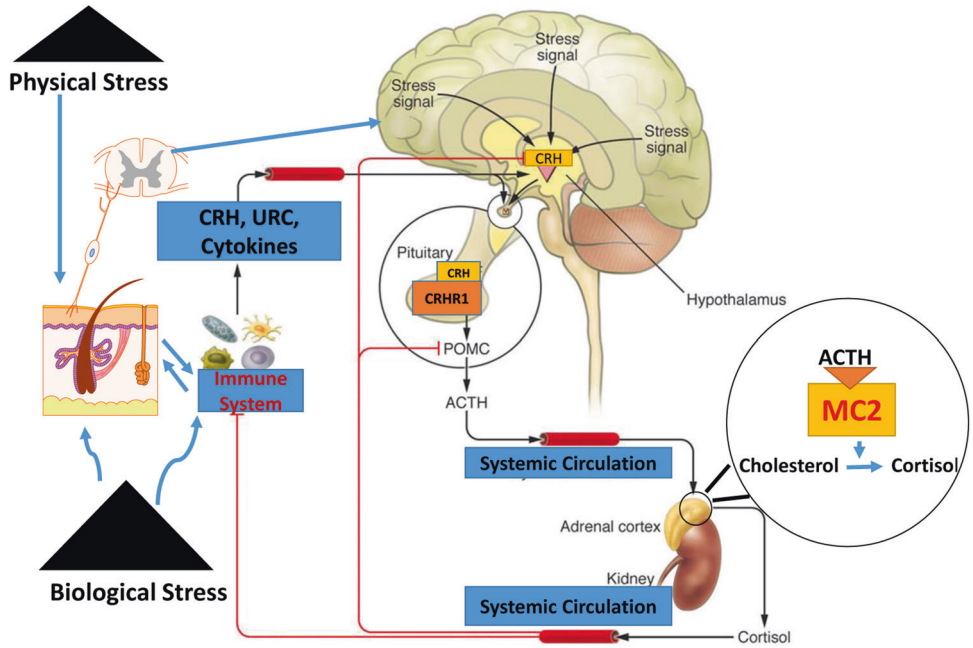

Fig. 2 The functional organization of the hypothalamic-pituitary-adrenal axis with inputs from the immune system and the skin. Physical and biological stress promotes the release of stress signals in both the brain, the skin, and immune cells, resulting in the hypothalamic release of CRH, which in turn stimulates the release of ACTH and POMC expression and processing in the anterior pituitary. ACTH binds to the MC-2 receptor in the zona fasciculata of the adrenal cortex and stimulates the transport of cholesterol into the mitochondria and stimulates the production cortisol. Glucocorticoids not only regulate body homeostasis but also act in a negative feedback loop for CRH and POMC expression. Re-use of some elements of schematic figure from Dr Slominski Commentary [205] is with permission from the Journal of Clinical Investigation.

stress it is released to the hypophysial portal vessels and after entering the anterior pituitary gland, it binds to the CRH receptor type 1 (CRH-R1) on the corticotrophs. Here it stimulates the expression, synthesis, and processing of proopiomelanocortin (POMC) including production and release of ACTH from corticotrophs [61–64]. After entering the circulation, ACTH binds to the G-protein coupled 7-transmemebrane receptor, MC-2 (melanocortin type 2 receptor), in the zona fasciculata of the adrenal cortex. Then, via cAMP dependent mechanisms it stimulates the transport of cholesterol into the mitochondria and the synthesis and activity of steroidogenic enzymes resulting in increased production and secretion of cortisol and corticosterone [65, 66]. Glucocorticoids inhibit POMC expression, ACTH secretion and production of CRH in a negative feedback loop [67]. Figure 2 shows a scheme for the regulation of the HPA axis.

Corticotropin releasing hormone (CRH)

In the central HPA axis, various stressors cause the release of CRH from the hypothalamus, which then indirectly regulates immune and inflammatory reactions through secretion of ACTH from the pituitary which subsequently stimulates glucocorticoid secretion by the adrenal glands [68]. Inflammatory cytokines, including IL-1, TNFα, and IL-6, stimulate the hypothalamus to secrete CRH [69]. CRH is also produced in various peripheral tissues including immune cells [70], skin [71], and other organs [72, 73]. The net effect of central CRH is immunosuppressive through activation of the HPA axis, while the direct effect of locally produced CRH is pro-inflammatory [70, 71, 74–76]. However, indirect immunosuppressive effects through stimulation of local production of POMC peptides and glucocorticoids are possible [77–80].

CRH, in addition to acting on CRH-R1 also acts on CRH-R2, and both receptors are widely distributed in the body [81, 82] including skin [71, 83] and the immune system [84]. CRH receptors are coupled to different second messengers including cAMP, IP3 (inositol triphosphate), and Ca^{2+} [71, 81]. There are different alternatively spliced isoforms of CRH-R1 and CRH-R2 with different functions [71, 79, 81, 85, 86]. CRH related peptides including urocortin 1–3 are also produced centrally and peripherally and these show different affinities for CRH-R1 and CRH-R2 [87, 88].

Adrenocorticotropic hormone (ACTH)

ACTH is synthesized as a part of the ~30 kD POMC precursor that undergoes cell-specific post translational

processing by protein convertase 1 (PC1) to cleave the 39 amino acid (aa) ACTH peptide, as well as other neuropeptide precursors that are further processed by PC2 to melanocyte stimulating hormone-γ (γ-MSH), β-MSH and β-endorphin peptides [64, 89]. ACTH can also be cleaved by PC2 and further processed to produce the 13aa α-MSH peptide. ACTH interacts not only with MC-2 as an exclusive ligand for this receptor, but also with other MC receptors (MC1, MC3-5) to regulate different functions including melanogenesis (via MC-1) [90–92]. ACTH can also act directly as an immunosuppressor [64, 93].

Glucocorticoid receptor

The glucocorticoid receptor (GR; NR3C1), a member of the nuclear receptor superfamily, mediates the action of glucocorticoids. It contains 4 domains: an N-terminal transactivation domain (NTD), central DNA-binding domain (DBD), a C-terminal ligand binding domain (LBD), and a hinge domain that connects the DBD with the LBD [52, 94–96]. There are two signaling pathways for GR: classical and non-classical [94, 97, 98]. GR is localized to the cytoplasm in association with a chaperone complex. In the classical GR signaling pathway, interaction with activating ligands induces a conformational change in GR and dissociation from the chaperone complex. GR subsequently translocates into the nucleus where it binds to GRE (glucocorticoid-responsive elements) and regulates the transcription of target genes [94, 97]. The non-classical GR signaling pathway is characterized by rapid signaling, which is transcription independent, and is dependent on various types of kinases [98].

Selected autoimmune and skin inflammatory disorders: an overview

Multiple sclerosis (MS)

MS is a chronic autoimmune disease that affects the central nervous system [99, 100]. MS affects about 1 in 400 adults with women being twice as likely to be affected by the disease than men [101, 102]. One likely mechanism giving rise to MS is that the overactive T helper cells (Th1 and Th17 cells) promote inflammation that results in demyelination [103]. The demyelination leads to the damage of the blood brain barrier, thus resulting in immune cells such as macrophages, T cells, and B cells infiltrating the brain and causing further inflammation and the eventual formation of scar tissue [103, 104].

The main types of MS are relapsing/remitting MS (RMMS), secondary-progressive MS (SPMS), primary progressive MS (PPMS), and progressive- relapsing MS [103, 105, 106]. Progressive- relapsing MS used to be a subtype, but in 2013 was removed due to it being considered as repetitive [105]. RMMS is the most common type of MS representing about 85% of MS cases, followed by PPMS which represents 8–10% of MS cases [103].

Lupus erythematous

Systemic lupus erythematosus (SLE) is an autoimmune disease that presents with multiple symptoms; however, the effects of the disease seem to result from the formation and deposition of autoantibodies [107–109]. The causes of the disease remain to be further investigated; however, there are multiple etiological factors (genetic, immunological, hormonal, etc) involved in the disease [107, 110]. The disease seems to be related to the dysregulation of the Th2 cells as there is an increase in Th2 cytokines (IL-4, IL-5, and IL-13) in SLE patients [108]. SLE also happens to affect females more than men [110, 111]. Fortunately, because of better treatment the survival rate for SLE has improved significantly from a 5% survival rate over a 5 year period in the 1950s to a 99% survival rate over a 5 year period in the 2010s [111].

Rheumatoid arthritis (RA)

RA is an autoimmune disease that is present in 1% of the population [112]. This disease adversely affects the quality of life and productivity of the patient, and there are high costs for therapy and its monitoring for toxicity [113]. RA is characterized by chronic synovitis, which shows a predilection for diarthrodial joints, particularly the metacarpophalangeal (MCP) and proximal interphalangeal joints (PIP joints) [112]. A preponderance of evidence indicates that an antigen-driven immune process against one or more proteins found in cartilage sustains synovial inflammation in RA [114, 115]. Each DMARD and biologic used to treat RA has the potential to cause unique serious adverse events and morbidities or mortalities. These include lung fibrosis, fulminant infections, inflammatory demyelination, liver cirrhosis, development of skin cancer or melanoma, retinal damage and triggering the onset of other autoimmune diseases such as vasculitis, MS and SLE [112, 116–120].

Psoriasis

Psoriasis is a chronic inflammatory disorder of the skin affecting 1–9% of the population [121–123]. The etiology of this diseases is multifactorial with a crucial role assigned to the malfunctioning of the immune system with the dysregulation of T cells, particularly of the Th1 and Th17 lineages [121, 123, 124]. Although the exact mechanisms need further investigation, it is accepted that the disease

progression is driven by cytokines, particularly IL-17 and IL-23 [123, 124]. In addition, stress and deregulation of local and systemic neuroendocrine functions have been implicated in the etiology and natural history of psoriasis [71, 125–127]. Currently, the main treatment for mild psoriasis encompasses the use of corticosteroids with or without additional topical vitamin D derivatives [128]. Ultraviolet light therapy is also used to treat psoriasis [129]. More recently, biologics that can target the IL-23/IL-17 pathways as well as JAK inhibitors that target IL-12 and IL-23 cytokines have been used in the therapy of this disease [130, 131].

Atopic dermatitis (AD)

AD is the most common skin inflammatory disease, affecting millions of people [132]. Like psoriasis the exact mechanism of this disease needs to be further investigated, although some of its causes include dysregulation of filaggrin and epidermal barrier function, and dysregulation of Th1 and Th2 effector cells [132, 133]. The acute phase of AD is mediated by Th2, while the chronic phase is mediated by Th1 cells [133]. Treatments for AD include the use of corticosteroids, cyclosporine, and more recently biologics that target IL-5 and IL-13, and potentially JAK inhibitors [131].

Expression of CRH and POMC in the immune system and the skin

Immune system

Peripheral CRH can be synthesized by cells of the immune system, somatic cells and by peripheral afferent type sensory fibers and postganglionic sympathetic nerves [134, 135]. Many tissues (e.g. skin, synovium of patients with RA, colonic mucosa of patients with ulcerative colitis, ovaries, cardiovascular system, eyes, uterus, adipose tissue, thymus, bladder, liver, stomach and kidney) express CRH and/or CRH receptors (CRHR) [64, 136–145]. The most extensively studied site has been the skin of humans and mice which revealed the presence of not only CRH and CRH-R1/2, but also peptides derived from POMC [64].

Whether an HPA-like axis is present and operative in synovium, gastrointestinal tract or other extracranial locations requires further studies. Although some authors reported expression of a truncated POMC mRNA in fibroblasts from human synovium, they failed to detect POMC protein in osteoarthritis synovial tissue and proper melanocortin signaling [146]. However, latter studies by these authors indicated a role for POMC signaling including MSH and ACTH in osteoarticular tissues with anti-inflammatory actions [147, 148]. Also, truncated *POMC* mRNA can be translated into full-length POMC protein that is processed to the corresponding downstream neuropeptides [149–151]. The POMC-derived peptides, ACTH and β-endorphin (β-End), are expressed in the synovium of RA patients and are produced by lipopolysaccharide stimulated B lymphocytes [152]. Analysis by double immunostaining of arthritic synovial tissue from Lewis rats with adjuvant arthritis showed that both ACTH and CRH colocalized in fibroblast-like cells and in mononuclear cells [152]. Various stimulants or stressors including phytohemagglutinin, concanavalin A, and IL-2, induce lymphocytes to express *CRH* mRNA and/or CRH protein [153]. Human monocyte-derived dendritic cells produce *CRH* mRNA and protein when stimulated by the intestinal commensal bacteria *bacteroides vulgatus* and *fusobacterium varium* [154]. Production of PGE2 by explants of RA synovial tissue is increased in the presence of CRH [155].

Locally produced CRH modulates both pro-inflammatory and anti-inflammatory processes. This is supported by its ability to stimulate production of IL-6 from blood monocytes, increase leukocyte IL-1 and IL-2 secretion, suppress LPS- induced IL-1 and IL-6 by peripheral blood mononuclear cells, stimulate lymphocyte expansion and IL-2 receptor expression, inhibit splenocyte proliferation induced by IL-2, facilitate NK cell mediated cell lysis; and stimulate the of production of ACTH and B-END by leukocytes [156–161]. CRH induces macrophages and mast cells to produce and release VEGF, IL-1β and IL-6 [84] and human peripheral blood $CD14^+$ monocytes to produce TNFα and dysfunction of vascular endothelium [162]. CRH upregulates IL-4 production by human Th2 T cells, downregulates IFN-ɣ production by human Th1 T cells and downregulates IL-10 production by FoxP3- negative human peripheral blood T regulatory cells [163].

The different effects of CRH on inflammation and immune function may be influenced by different CRH receptors being expressed on different types of leukocytes or by somatic cells in different tissues [84]. The effects of CRH are mediated via two different receptors, CRH-R1 and CRH-R2, which are members of class B1 of G-protein coupled receptors that exhibit approximately 70% overall homology at the amino acid sequence level but only about 47% homology in the N-terminal extracellular domain [164]. CRH binds to CRH-R1 with greater affinity than it binds to CRH-R2 [165]. Alternative splicing gives rise to at least 8 spliced variants of CRH-R1 and at least 3 spliced variants of CRH-R2 [84, 85, 166]. Both the pro-inflammatory and anti-inflammatory effects have been reported to be mediated by either CRH-R1 or CRH-R2 indicating that the ultimate effect of signaling via these receptors is determined by factors other than the specific type of CRH-R. For example, CRH via CRH-R1 induces mast cells and macrophages to produce IL-6, IL-1β,

TNFα and VEGF and promotes vasculitis but has also been shown to block IL-1α-stimulated prostaglandin synthesis by fibroblasts [84]. Similarly, in the early stages of inflammation, CRH via CRH-R2, suppresses production of TNFα by macrophages activated by LPS, but has the opposite effect on LPS-induced macrophage TNFα production in late stage inflammation [167].

Skin

Since the initial detection of CRH, CRH-R1, and CRH-R2 in human [168–173] and murine [168, 174–176] skin, a flurry of reports documented their regulated expression in the mammalian skin (reviewed in [71, 79, 177–180]). CRH and urocortins acting on cutaneous CRH-R1 and CRH-R2 can affect skin functions in a context-dependent fashion [71, 75, 79, 181, 182]. The direct CRH effects are predominantly anti-proliferative, pro-differentiation, barrier building and pro-inflammatory. However, indirect effects through activation of POMC or glucocorticoid signaling can be anti-inflammatory [71, 79, 80] (see below). It should be noted that since the original discoveries on POMC expression and production of POMC peptides by skin cells [149, 183–185], it has been widely established that skin cells can produce different POMC peptides in a context-dependent fashion under different stimuli to regulate different skin functions, including downregulation of pro-inflammatory responses [64, 129, 178, 186].

Extra-adrenal glucocorticoid biosynthesis

General overview with a list of steroidogenically active organs

It has been reported that glucocorticoids can be synthesized in many non-adrenal and non-gonadal tissues, such as the brain, intestine, lung, skin, spleen, placenta, adipose tissue and the immune system, as well as in a variety of cancer cells [42, 52, 187–189]. Table 1 shows the distribution of the proteins involved in the initial rate-controlling steps of steroidogenesis, CYP11A1 and StAR, as well as other downstream steroidogenic enzymes reported to be in these tissues including immune cells (Fig. 3), at least at the level of mRNA expression. Some of the tissues listed such as bone, endometrium and mammary gland appear to primarily produce sex steroids and the production of corticosteroids from cholesterol remains to be established.

Glucocorticoid biosynthesis in the skin

The skin has been shown to express all the CYP enzymes involved in steroid synthesis, including CYP11A1, CYP17A1, and CYP21A2 and StAR protein in both keratinocytes and sebaceous glands [188, 190–193] (Table 1; Fig. 4). Moreover, the skin has also been shown to express CRH and POMC [170]. The incubation of melanocytes with CRH caused the melanocytes to produce ACTH, and in turn ACTH stimulated the production of cortisol in melanocytes [78]. Similarly, fibroblasts can produce cortisol as shown by liquid chromatography/ mass spectrometry (LC/MS) [194], and production of corticosterone can be stimulated by CRH and ACTH. Finally, the exposure of dermal fibroblasts to CRH stimulates POMC activity and corticosterone production [77], with ultraviolet B (UVB) activating cutaneous elements of the HPA [195–198]. Thus, there is evidence that a functional peripheral HPA-like axis is operative in the skin [199, 200].

Glucocorticoid production in the skin is regulated by CRH, ACTH, IL-1β, UV light, and by 11βHSD1 and 11βHSD2 enzymes [52, 188, 192]. Stress to the skin either by inflammation or injury causes the stimulation of ACTH and POMC production in the skin [64]. UVB exposure of the skin has been found to cause production of CRH, ACTH, β-END, and cortisol [195]. The corticosteroids produced in the skin appear to play a role in countering the inflammatory response of the skin [192, 201]. However, glucocorticoids produced locally can have a negative effect on barrier function and would healing and promote skin infection [202–206].

Glucocorticoid biosynthesis by the immune system

The thymus, a place where T lymphocyte maturation occurs, has been found to produce glucocorticoids [187] (see Table 1). In fact, de novo synthesis of steroids in the thymus was discovered in the mid 1990s by Vacchio et al. [207]. Vacchio also demonstrated the presence of the steroidogenic enzymes CYP11A1 and CYP11B1 by immunohistochemistry. In addition, thymic epithelial cells produced pregnenolone and deoxycorticosterone. Peripheral T cells have also been reported to produce steroids, particularly pregnenolone [208]. Importantly, there are recent reports showing the expression of CYP11A1 in human [209] and murine [208, 210, 211] T cells. We have also observed the expression of CYP11A1 in CD4 and CD8 human T lymphocyte and non-T cells (B cells and monocytes) as shown in Fig. 3.

The role of the glucocorticoid receptor in the immune system

Inhibition of the expression of pro-inflammatory cytokines and synthesis by glucocorticoid is mediated by the binding of the glucocorticoid-GR complex to GREs in the promoter regions of these genes (e.g. IL-1α and IL-1β). This can

Table 1 Extra-adrenal and extra-gonadal expression of CYP11A1, StAR and other steroidogenic enzymes.

Tissue or cell type[a]	CYP11A1 expression	StAR expression	Other steroidogenic enzymes expressed[b]	Major type(s) of steroid produced	References
Adipocytes (human subcutaneous abdominal and omental and/or mouse 3T3-L1 preadipocytes)	mRNA, protein, activity	mRNA	CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP21A2, HSD3B1, HSD11B1, HSD17B3, HSD17B5, HSD17B7; SRD5A2	Sex steroids, corticosteroids	[254–256]
Bone, osteoblasts	mRNA, protein	Not investigated	CYP17A1, CYP19A1, HSD3B, HSD17B2, HSD17B4	Estrogens	[257–259]
Brain	mRNA, protein, activity	mRNA, protein	CYP11B1, CYP17A1, CYP21A2, CYP2D6 (21-hydroxylase), HSD3B, HSD11B2	Pregnenolone sulfate, DHEA-sulfate, corticosteroids	[1, 19, 189, 260–264]
Colorectal, intestine (non-cancerous and cancerous)	mRNA, protein, activity	mRNA	CYP11B1, CYP21A2, HSD3B3, HSD11B1, CYP17A1 (human tumor)	Corticosterone (mouse), cortisol	[189, 265–271]
Endometrial, endometriosis and tumors	mRNA, protein, activity	mRNA, protein	CYP17A1, CYP19A1, HSD3B2	Progesterone, androgen, estrogen	[272–274]
Heart (and blood vessels)	mRNA	mRNA	CYP11B1? CYP11B2? CYP21A2, HSD3B, HSD11B2	Aldosterone?[c] corticosterone (mouse)	[189, 275–279]
Kidney (rat)	mRNA protein, activity	mRNA, protein	HSD3B	Pregnenolone, progesterone	[280, 281]
Lung	mRNA, activity	mRNA	CYP11B1, CYP21A2, HSD3B1, HSD3B3, HSD11B1	Aldosterone, corticosterone (mouse)	[265, 282, 283]
Lymphocytes macrophages and monocytes	mRNA, protein, activity	mRNA, protein	CYP21A2	Pregnenolone, cortisol?	[209, 284–288]
Mammary gland (including tumors)	mRNA	mRNA, protein	CYP17A1, CYP19A1	Progesterone, estrogen	[8, 18, 289–291]
Nasal mucosa	mRNA, protein, activity	not investigated	CYP11B1, CYP21A2, HSD3B, HSD11B1, HSD11B2,	Cortisol	[292, 293]
Pancreas	mRNA, protein	mRNA, protein	CYP11B1	Pregnenolone? cortisol?	[294, 295]
Prostate	mRNA, protein, activity	mRNA, protein	CYP17A1, CYP19A1 HSD3B1, HSD3B2, HSD17B3, HSD17B5	Progesterone, androgens	[296–300]
Skin	mRNA, protein, activity	mRNA, protein	CYP11B1, CYP17A1, CYP21A2, HSD3B1, HSD11B1, HSD11B2, HSD17B	Corticosteroids, androgens	[19, 188, 232, 301]
T cells-activated (mouse)	mRNA, protein, activity	not investigated	not investigated	Pregnenolone, corticosterone?	[208, 210, 211, 270, 302, 303]
Thymus (mouse) thymocytes and thymus epithelial cells	mRNA, activity	mRNA	CYP11B1, CYP17A1, CYP21A2, HSD3B	Corticosterone	[189, 207, 208, 304]

[a]Refers, at least in part, to human tissues unless otherwise indicated.

[b]Expression observed at least at the level of mRNA.

[c]Question mark indicates product is predicted but not confirmed experimentally.

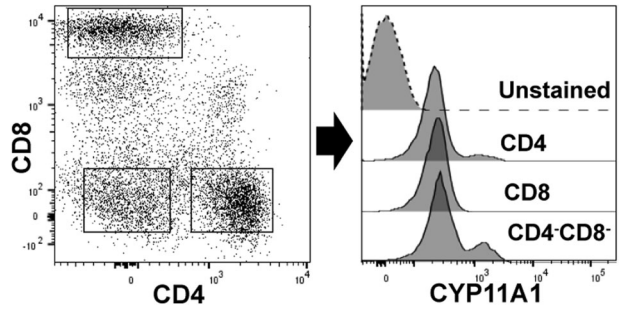

Fig. 3 CYP11A1 expression in human peripheral blood mononuclear cells (PBMCs). The left dot plot shows CD4, CD8 T cells, and $CD4^{-}CD8^{-}$ cells in PBMCs. The right histogram shows expression of CYP11A1 in gated CD4 cells, CD8 T cells, and $CD4^{-}CD8^{-}$ cell populations verses the unstained PBMC. The blood was obtained from a healthy volunteer (IRB 160426001) and processed as described previously [250]. Intracellular staining for CYP11A1 (Cell signaling technology; Danvers, MA, USA) was performed in cells fixed with paraformaldehyde and permeabilized in methanol containing buffer [250, 251]. Anti-CYP11A1 was conjugated to APC-Cy7 (Abcam; Cambridge, UK) as per manufacturers protocol before use. Stained cells were analyzed using a BD-FACS Symphony flow cytometer (BD Biosciences, San Jose, CA). Data are representative of three independent experiments utilizing different donors.

block the binding and function of other transcription factors (e.g. nuclear factor-kappa-B (NF-κB), and activator protein-1(AP-1)) essential for transcriptional activation of proinflammatory mediators [212–216]. Inversely, NF-kB can also inhibit the function of the GR in a dose- dependent manner [217] indicating that these pathways mutually affect each other. The protein glucocorticoid-induced leucine zipper (GILZ) has been found to play a role in some of the anti-inflammatory effects of glucocorticoids [218–220]. These effects include, but are not limited to inhibiting NF-κB, Ras/Raf, and AP-1 dependent pathways [218, 220, 221].

Another mechanism for glucocorticoid-GCR mediated inhibition of inflammation is the recruitment of other transcription factors to promoter sequences of genes that code for proteins with anti- inflammatory properties (e.g. IL-10, NF-κB, IL-1 RII, GILZ, lipocortin-1, alpha-2-macroglobulin, and secretory leukocyte-protease inhibitor) [212–214, 220, 221]. Glucocorticoids can also mediate their anti-inflammatory effects at the post-translational level by decreasing the stability of mRNAs for IL-1,IL-2, IL-6, IL-8, TNFα and GMCSF, or increasing the stability of a number of other mRNAs. The latter include mRNAs for various enzymes (e.g. angiotensin - converting enzyme and neutral – endopeptidase) that degrade the vasodiliatory peptide (e.g. bradykinin), annexin-1(lipocortin-1, macrocortin and/or lipomodulin) which has anti-inflammatory action by inhibiting phospholipase A2 leading to reduced generation of arachidonic acid from membrane phospholipids, and by decreasing the stability of cyclooxygenase-2 mRNA resulting in reduced production of PGE2 [222].

The global effects of glucocorticoids on leukocytes and endothelial cells lead to a decrease in the adherence of leukocytes to the endothelium of blood vessels which reduces their extravasation into areas of inflammation, thus reducing the inflammatory response [223–225]. Proliferation of B cells and T cells is inhibited as well as the production of immunoglobulins (B cells) and Th1 and Th2 cytokines (T cells). There is less inhibition of Th2 production than Th1 and there is attenuation of natural killer (NK) cell activation [177, 226, 227]. Glucocorticoids act on eosinophils to increase their apoptosis directly, or via reducing the production of IL-5 [228]. Mast cell degranulation, cytokine production and their adherence to the endothelium are inhibited by glucocorticoids [177, 229]. Glucocorticoids reduce the number of circulating monocytes and cause activation of antigen presentation functions of monocytes/macrophages/dendritic cells [177, 230].

Dysregulated local glucocorticoid synthesis in the etiology of autoimmune and inflammatory disorders

Skin inflammatory disorders

Psoriasis and AD

The dysregulation of skin steroidogenesis may play a role in both psoriasis and AD [188, 231, 232]. Glucocorticoids act by blocking the production of IL-4 and IL-5 [231, 233]. Hannen et al. reported that in the skin, the expression of several enzymes involved in steroid synthesis such as CYP11A1 and CYP17A1 are reduced in psoriasis, as well as the enzymes 11βHSD1, 11βHSD2, and the GR [128]. They further demonstrated that StAR and MLN64 expression is reduced in skin of both AD and psoriasis patients [193]. Tiala et al. reported that CCHCR1, a gene that plays a role in steroidogenesis and vitamin D metabolism, is downregulated in psoriasis [234]. Another study reported that deficient in situ synthesis of glucocorticoids in psoriatic skin was associated with increased inflammation [235]. The above data support the hypothesis that defective glucocorticoid signaling contributes to the pathogenesis of psoriasis [206].

Autoimmune disorders

Multiple sclerosis (MS)

Local steroidogenesis might also play a role in the prevention of MS. Boghozian et al. found lower CYP17A1 expression levels as well as lower dehydroepiandrosterone (DHEA) levels in oligodendrocytes in both MS patients and

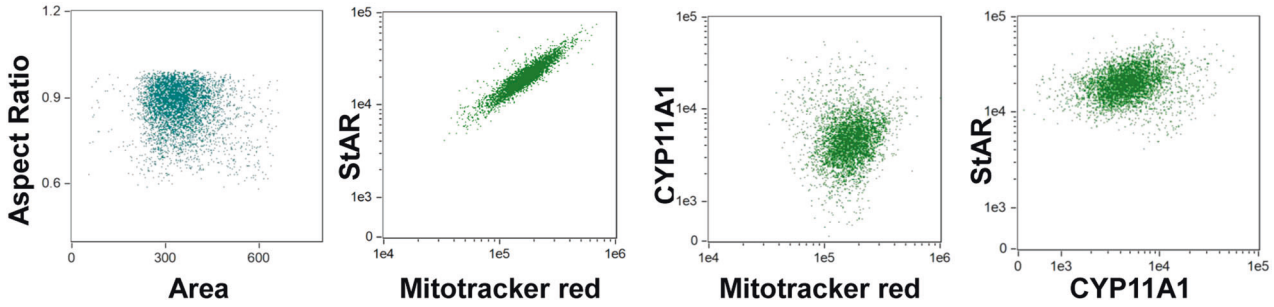

Fig. 4 Expression of StAR and CYP11A1 in HaCaT cells (human epidermal keratinocytes). The intracellular expression of StAR and CYP11A1 in HaCaT cells was determined using Image Stream II (Amnis, Seattle, WA, USA) cytometer as described previously [252]. Dot plots from left to right depict Area vs Aspect ratio (strategy to gate on single cells); StAR vs mitochondria; CYP11A1 vs mitochondria; and StAR vs CYP11A1. The 1:1 (diagonal) expression of StAR with mitochondria indicated their tightly linked expression and potential co-localization. Positive correlation between expression of CYP11A1 and mitochondria and between StAR and CYP11A1 indicate linked expression with each other and perhaps co-localization in the mitochondria. The HaCaT keratinocytes were detached and processed as previously described [253]. The cells were fixed and stained with antibodies to CYP11A1 (Cell signaling technology; Danvers, MA, USA) StAR (Santa Cruz; Dallas, TX, USA), and Mitotracker Red (CMX Ros Invitrogen; Carlsbad, CA, USA) at 10 nM as described previously [252]. Data were analyzed using IDEAS software (Amnis, Seattle, WA, USA).

animals with EAE (experimental autoimmune encephalomyelitis) [236]. This group also found increased expression of IL-1β and IFN-γ in MS patients. The results seem to suggest that DHEA may play a role in immunoregulation. Arnason et al. reported that ACTH can be beneficial for MS patients, although Miller et al found ACTH to be a candidate for the therapy of MS as early as 1961 [237, 238]. Arnason et al. later described how melanocortins are anti-inflammatory and act by blocking NF-kB, and that melanocortins exert their anti-inflammatory effects through melanocortin receptors MC1R, MC3R, and MC5R [237].

The expression of genes encoding certain enzymes producing sex hormones as well as the receptors for these hormones may also be implicated in the pathogenesis of MS [101]. For example, Luchetti et al. reported that the MS lesions in males display higher expression of mRNA for aromatase, estrogen receptor B, and TNF, while women with MS have increased expression of mRNA for 3β-hydroxysteroid dehydrogenase and the progesterone receptor [101].

Lupus erythematous

The dysregulation of steroidogenesis could be a contributing factor to the pathogenesis of SLE. Corticosteroids are used in first line treatment of patients with SLE [108, 188, 239]. Glucocorticoids affect T cells (especially CD4) more rapidly than B cells [239]. Glucocorticoids affect the T cells by enhancing circulatory emigration, inducing apoptosis, inhibiting T cell growth factors, and impairing the release of cells from lymphoid tissue [239]. ACTH has been used since the 1950s as a treatment option for SLE [240, 241]. Vogl et al. have found that a number of steroids are lower in SLE patients than control patients, specifically progesterone, 17-hydropregnenolone, and cortisol [242]. Li et al. compared pituitary hormone level in SLE patients verses the healthy controls and found that prolactin levels were increased in SLE patients [110].

Rheumatoid arthritis (RA)

Steroidogenesis as well as the factors that regulate it may play an important role in the pathogenesis of RA. This is not surprising since 100–2000 genes are regulated by glucocorticoids [243]. Yoursi et al. found that there are 32 steroid-like metabolites whose concentration differ significantly between RA patients and healthy controls [244]. These metabolites included DHEA, adrostenediol, and cortisol [244].

Straub et al. reported that serum levels of cortisol, DHEA, and DHEA-S levels were elevated in early RA patients compared with healthy individuals and correlated with elevated levels of the proinflammatory cytokines, IL-6 and TNF [245]. This group speculated that this might be due to RA patients having a deficiency in either CYP21A2 or CYP11A1 [245]. In another report, Straub et al. noted that the relatively low levels of steroids in RA patients in relation to proinflammatory cytokines was not due to increased renal clearance, and in fact the renal clearance of steroids, including androgens, was decreased in RA patients [246].

Schlaghecke et al. found that the PBMCs (peripheral blood mononuclear cells) in RA patients have a lower density of glucocorticoid receptors that healthy controls [247]. However, Schlaghecke later reported that this decreased GC density does not cause glucocorticoid resistance in RA patients [248].

In a review article about the role of 11βHSD1 and 2 in RA, Edwards concluded that overactivity of 11βHSD1 can cause dysregulation of the HPA controlling cortisol

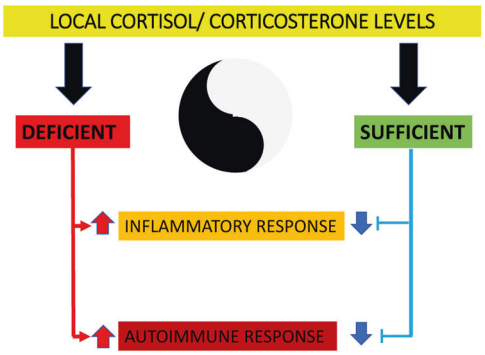

Fig. 5 Local cortisol/corticosterone levels can control immune functions and inflammatory responses in a Yin/Yang manner.

production [249]. He also speculated that the proinflammatory cytokine, TNFα, triggers the overactivity of 11βHSD1 and that anti-TNFα therapy can be beneficial in RA [249]. Finding out the exact mechanism by which steroidogenesis is dysregulated in RA may open doors for discovering new treatment options in RA. Specifically, the regulation of the local interconversion of cortisol and cortisone and/or glucocorticoid biosynthesis and CYP11A1 activity may be targeted in immune cells or their target organs.

Concluding remarks and future perspectives

Glucocorticoids play many roles in the maintenance of homeostasis in the body including displaying important immunosuppressive activity. Glucocorticoid synthesis is regulated by ACTH, CRH, and cytokines such as IL-1, IL-6 and TNFα in a context-dependent fashion. While some of the regulators such as ACTH directly display immunosuppressive effects, others such as CRH and cytokines have predominantly pro-inflammatory activity. Therefore, in peripheral organs dissociation of the actions of the higher-level regulators, CRH, and proinflammatory cytokines, from the executive arm involving the synthesis of glucocorticoids, can lead to uncontrolled stimulation of the immune system. Furthermore, our view is that dysregulation of local (immune cells and or target organs for immune activity) glucocorticoid synthesis plays a pivotal role in several autoimmune diseases, including MS, LE, and RA, as well as proinflammatory skin diseases such as psoriasis and AD (Fig. 5).

Creative investigations on how to pharmacologically target local and endogenous glucocorticoid biosynthesis and glucocorticoid signaling should help to find future therapies/cures for inflammatory and autoimmune diseases. In particular, there needs to be targeted research aimed at increasing local cortisol/corticosterone levels through the activation of their local synthesis without systemic effects and/or by preventing their inactivation, and/or by stimulation of the activity of 11βHSD1/2. The precise delivery of factors regulating glucocorticoid biosynthesis to the target organs or immune cells should also be a focus of future research. Such agents that are able to directly or indirectly influence local cortisol levels may be chemically synthesized in an educated fashion or represent natural products identified by medicinal chemistry and computer modeling. In addition, the application of different types of physical factors such as ultraviolet B (UVB) radiation in a controlled fashion may represent an additional opportunity, since UVB is both immunosuppressive and also stimulates glucocorticoid biosynthesis. In conclusion, local cortisol levels can influence the development or regression of inflammatory (psoriasis, AD) and autoimmune diseases such as LE, MS and RA. Research aimed at modulating local levels of cortisol is necessary to provide new therapies to patients suffering from these devastating diseases.

Acknowledgements The study was supported by NIH grants 1R01AR073004-01A1 and R01AR071189-01A1 and by a VA merit grant (no. 1I01BX004293-01A1) to ATS, internal (UAB) funds to ATS and CR and by the Intramural Research Program of the NIH, the NIEHS, NIH Z01-ES-101585 (to AMJ).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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