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Endometriosis Pathoetiology and Pathophysiology: Roles of Vitamin A, Estrogen, Immunity, Adipocytes, Gut Microbiome and Melatonergic Pathway on Mitochondria Regulation

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Abstract: Endometriosis is a common, often painful, condition that has significant implications for a woman's fertility. Classically, endometriosis has been conceptualized as a local estrogen-mediated uterine condition driven by retrograde menstruation. However, recent work suggests that endometriosis may be a systemic condition modulated, if not driven, by prenatal processes. Although a diverse array of factors have been associated with endometriosis pathophysiology, recent data indicate that the low body mass index and decreased adipogenesis may be indicative of an early developmental etiology with alterations in metabolic function crucial to endometriosis pathoetiology.

The present article reviews the data on the pathoetiology and pathophysiology of endometriosis, suggesting key roles for alterations in mitochondria functioning across a number of cell types and body systems, including the immune system and gut microbiome. These changes are importantly regulated by decreases in vitamin A and its retinoic acid metabolites as well as increases in mitochondria estrogen receptor-beta and the N-acetylserotonin/melatonin ratio across development. This has treatment and future research implications for this still poorly managed condition, as well as for the association of endometriosis with a number of cancers.

Keywords: endometriosis; vitamin A; melatonin; prenatal; adipogenesis; immune; microRNA; Cytochrome P450 1B1; TrkB; N-acetylserotonin.

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Introduction

Endometrial tissue is usually restricted to the uterus. In endometriosis, however, endometrial tissue can grow in other locations, including the ovaries and fallopian tubes, as well as in nearby and more distant tissue. Consequently, the endometrial tissue in these other areas can result in inflammation and scarring [1]. Pelvic pain is usually the main presenting symptom, being chronic in 50% of patients, with 70% experiencing pelvic pain during menstruation. Infertility is common, being evident in approximately 50% of people presenting with endometriosis [2]. Between 5-10% of western women and about 15% of Asian women will experience endometriosis, most typically with a first presentation at 30-40 years, often as a consequence of difficulties in conceiving [1].

Factors linked to endometriosis pathophysiology include: increased oxidative and nitrosative stress (O&NS), chronic immune inflammation, increased immune tolerance, autoimmunity, t helper (Th)17 cells and interleukin (IL)-17, as well as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) associated activation of the aryl hydrocarbon receptor (AhR) [3]. Estrogen at the estrogen receptor-alpha (ERα) can exacerbate symptoms, with estrogen also having regulatory, and symptomatic, effects via the ERβ. As both of these estrogen receptors can be mitochondria-located, there can be significant changes in mitochondria functioning in endometriosis. Raised O&NS in endometrial tissue is overly compensated by an ERβ-mediated increase in mitochondria superoxide dismutase (SOD)2, leading to mitochondria with heightened levels of oxidative phosphorylation and ATP production. Within mitochondria cytochrome P450 (CYP)1B1 is increased [4], as often occurs in many cancers. Increased brain-derived neurotrophic factor (BDNF) [5] and the activation of its receptor, TrkB, are also associated with endometriosis [6]. As such, endometriosis shows alterations in mitochondria

functioning, oxidative stress regulation and increased trophic factors, linking endometriosis with tumor-associated pathophysiology.

Endometriosis, like a growing number of other medical conditions [7], shows alterations in the gut microbiome [8]. The raised levels of depression in endometriosis may be linked to this, given the gut microbiome's role in depression pathoetiology, especially via a decrease in the short-chain fatty acid (SCFA), butyrate [9]. Very high levels of depression are often evident in women with chronic pelvic pain compared to those with endometriosis who are pain free [10]. As such, some of the biological heterogeneity in endometriosis may be mediated by variations in the levels of pain-linked depression- and stress-induced gut dysbiosis and associated increases in gut permeability.

The current article reviews this diverse array of data on the pathoetiology and pathophysiology of endometriosis and proposes an etiological role for prenatal factors, with an increase in the mitochondria N-acetylserotonin (NAS)/melatonin ratio proposed to link the wide array of previously disparate pieces of data pertaining to endometriosis pathophysiology. Decreased adipocyte levels also have a significant role, within the context of a gut-hepatic-adipocyte-hypothalamus axis, with exosomes being important effectors of change by this axis, due primarily to their differential priming of immune cells. Such a frame of reference better integrates wide bodies of data on the pathoetiology and pathophysiology of endometriosis, including its association with heightened cancer risk.

Endometriosis: Pathophysiology

A wide array of pathophysiological processes have been linked to endometriosis, many of which are shared with other conditions, including increased O&NS, and immune-inflammation. This section summarizes the main bodies of data pertaining to endometriosis pathophysiology.

Oxidative and Nitrosative Stress (O&NS)

Increased levels of O&NS are evident in endometriosis, with O&NS facilitating ectopic endometrium implantation [11, 12]. Heightened levels of O&NS positively correlate with symptom severity [13]. Consequently, a wide array of antioxidants and antioxidant inducers, including vitamins C, vitamin E, melatonin, resveratrol, xanthohumol and green tea's epigallocatechin- 3-gallate can afford some symptomatic relief in endometriosis [11]. Heightened O&NS may be mediated by stress- and pro-inflammatory cytokine-induced gut dysbiosis and increased gut permeability.

Immune Activation

Across different medical conditions, increased O&NS is commonly associated with higher levels of immune-inflammatory activity and pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, IL-17 and IL-18 [14]. This is similar in endometriosis, with heightened IL-1β and IL-18 levels, linked to oxidative stress-induction of the Nod-like receptor family pyrin domain containing (NLRP)3 inflammasome, which correlates with poor survival upon transition to endometriosis-associated ovarian cancer [15]. IL-10 levels are also increased in endometriosis, mediated by increases in regulatory T (Treg) cells, which become increasingly evident over endometriosis progression [16]. These authors also found increased levels of transforming growth factor (TGF-β) in the peritoneal fluid and the serum. An increase in the anti-inflammatory cytokine, IL-37, in the peritoneal fluid has also been shown in endometriosis, with this cytokine thought to contribute to a decrease in inflammatory activity [17]. As such, a mixed immune response is evident in endometriosis, with both pro- and anti-inflammatory components.

A number of immune cell subtypes are altered in endometriosis, including: increased Treg cells in the peritoneal fluid coupled to increased TGF-β and a relatively lower percentage of Th17 cells in both the peritoneal fluid and peripheral blood, with these changes positively correlating with severity [18]. However, other data shows Th17 to be increased in the peritoneal fluid and blood in endometriosis, also in correlation with levels of severity [19]. Such contrasting results are seen to reflect endometriosis heterogeneity, although it may more likely reflect the complex sets of dynamic interactions of immune cell types and factors that act to regulate them, as well as reflecting changes in other systems, such as stress and pro-inflammatory cytokines increasing gut permeability, which can drive wider immune cell changes. Heightened levels of Th17 cell activity also increases the activation of IL-17 producing gammaDelta t cells (γδ-T cells), which are another major contributor to circulating IL-17 levels. This may be particularly relevant in circumstances where gut permeability is increased, given the high levels of γδ-T cells in proximity to the gut [20]. Overall, the heightened levels of pro-and anti-inflammatory cytokines and immune cells may reflect dysregulation in the how inflammatory

and anti-inflammatory processes are regulated, as well as alterations in other immune regulatory processes, such the gut microbiome and gut permeability.

Aryl Hydrocarbon Receptor (AhR)

AhR activation is also important to endometriosis pathophysiology, with data suggesting that AhR single nucleotide polymorphisms (SNPs) modulate endometriosis risk [21]. AhR activation can have differential consequences in different cell types, including from different effects arising from exogenous versus endogenous and induced ligands [22]. As well as its regulatory effects, the AhR can significantly interact with, and modulate, many of the pathophysiological factors associated with endometriosis. Polychlorinated biphenyls (PCBs), with a dioxin-like structure that activate the AhR, increase levels of estrogen and 17β-hydroxysteroid dehydrogenase (HSD)-7 activity as well as pro-inflammatory cytokines in a murine model of endometriosis [23]. Antagonism of the AhR prevented such PCBs effects, suggesting a role for environmental toxins, via the AhR, in the pathophysiology of endometriosis. This is supported by similar data in a rodent model of endometriosis [24]. AhR expression on mast cells may also be important, with mast cells in close association with endometrial tissue [25].

Indoleamine 2,3-dioxygenase, Kynurenine and Melatonergic Pathways

Recent data shows endometrial tissue to have increased levels of pro-inflammatory cytokine-induced indoleamine 2,3-dioxygenase (IDO), leading to kynurenine pathway activation. Increased IDO and kynurenine are evident in endometrial tissue, with kynurenine activating the AhR in IL-17 and IL-10 positive mast cells [25]. IDO can also contribute to the metabolism of melatonin [26], contributing to decreased melatonin availability in endometrial tissue. As such, local regulation of AhR ligands by inflammation, as well as environmental factors, may contribute to AhR activity and IDO, with increased IDO expression and activity associated with an increase in the invasiveness of endometrial stromal cells [27]. It should be noted that, as with circulating pro-inflammatory cytokines, environmental toxin effects via the AhR are also likely to increase gut permeability, as well as mediate changes that are common across a number of cancers, including increasing CYP1B1 levels

Notably, pro-inflammatory cytokine-induced IDO drives tryptophan to the production of kynurenine and associated kynurenine pathway products, such as the neuroregulatory kynurenic acid and quinolinic acid, and away from serotonin, NAS and melatonin synthesis. Raised pro-inflammatory cytokines may also inhibit the circadian production of melatonin by the pineal gland [28]. The circadian dysregulation caused by shift work decreases pineal gland melatonin production and increases the risk of endometriosis [29]. Such data indicates a general suppression of melatonergic pathway activity in endometriosis. In a preclinical endometriosis model, the loss of melatonin following pinealectomy exacerbates endometriosis symptomatology [30]. It is this shift away from serotonergic and melatonergic pathways that also forms the biological underpinnings for heightened levels of depression in endometriosis [3, 31].

Gut Microbiome, Gut Permeability and Butyrate

Recent data indicates a role for gut dysbiosis in endometriosis, perhaps in association with alterations in vaginal and cervical microbiota [32], which is supported by preclinical model data [33, 34]. It requires investigation as to whether such gut dysbiosis is associated with an increase in gut permeability. This would seem likely, given that the increase in pro-inflammatory cytokines and pain-associated stress in endometriosis increase gut permeability [35, 36]. Such gut dysregulation is strongly linked to a decrease in the production of the SCFA, Butyrate, which has important roles in gut barrier maintenance, immune dampening, and optimizing mitochondria functioning. Butryate can also induce melatonin and has histone deacetylase (HDAC) inhibitory effects [37, 38]. All of these butyrate effects are likely to modulate endometriosis etiology and course as well as the transition to endometrial and ovarian cancer [39, 40], including inhibiting the self-renewal capacity of endometrial cancer stem cells [41]. This is supported by recent work advocating the utilization of HDAC inhibition in the treatment of endometriosis [42, 43], although there may be some association of HDAC3 inhibition and infertility [44].

Vitamin A and Retinoic Acids

Decreased vitamin A, and its retinoic acid metabolites, may also be relevant to endometriosis pathoetiology

and pathophysiology [45]. All-trans retinoic acid (ATRA) dramatically prevents the proliferation of endometrial tissue cysts, coupled to a decrease in local estradiol production [45]. Over the course of the menstrual cycle, changing patterns of steroid exposure modulate expression of retinoid receptors and ATRA synthesis. Local ATRA acts to correctively modulate the endometrial synthesis of many of the factors altered in endometriosis, including cytokines, differentiation, matrix metalloproteinase, secretion, connexin-43, and integrins [46]. ATRA biosynthesis seems impaired in endometriosis lesions, linked to a decrease in cellular retinol-binding protein type 1 (RBP)1 [46]. The regulation of vitamin A metabolites, including ATRA, is driven by endogenous enzymes induced by HDAC inhibitors, thereby suggesting modulation by gut-derived butyrate and other endogenous HDAC inhibitors [47]. As vitamin A increases microbiome-derived butyrate, vitamin A and other positive regulators of butyrate, will increase the protection afforded by ATRA. Vitamin A can increase the melatonergic pathways [48] as well as optimize mitochondria functioning [49]. ATRA prevents TGF-β + IL-6 from inducing Th17 cells [50], favouring increased Treg cells, thereby highlighting a role for vitamin A and its retinoic acid metabolites in the pro-/anti-inflammatory cytokine balance. Clearly, decreased vitamin A and its metabolites may be an important factor in the pathophysiology of endometriosis, given its regulatory interactions with other altered factors.

Lower vitamin A metabolite levels may arise from increased CYP26. Raised TGF-β levels in the serum and peritoneal fluid in endometriosis [16] would be expected to decrease CYP26, and thereby increase vitamin A metabolite availability [51]. This indicates that increased Treg cells would be co-ordinated with higher vitamin A metabolite availability, which is a link that seems to be broken in endometriosis, possibly from concurrent increases in pro-inflammatory activity and epigenetic HDAC activity [51]. Decreased vitamin A prenatally can significantly alter the development of the post-natal gut [52], and could act as a prenatal pathoetiological prime, in part via the impact of lower vitamin A on mitochondria and cellular regulatory functions.

Uterine Microbiome

There is a growing interest in the composition and role of the uterine microbiome, with likely relevance to endometriosis and its transition to cancer [53]. Cervical lesions seem associated with alterations in the uterine microbiome composition [54], which may vary in endometriosis and over the menstrual cycle [55]. Within individuals, there does seem some continuity within the vagino-uterine microbiome, perhaps arising from cyclical hormonal changes that act to modulate the pH, and therefore the conformation of cervical mucins [56]. A number of lifestyle and dietary factors correlate with the composition of the vagino-uterine microbiome, including herbal medication impacts [55]. The significance of this has still to be determined, including as to any impact on the wider processes and factors associated with endometriosis, such as ATRA regulation, mitochondria functioning and the melatonergic pathways or indeed as to whether there is a gut-uterus axis, maybe linked by dietary impacts or perhaps via exosomes or the micro-metastasis of endometrial cells, which have been found in the lung, brain and other organs in preclinical models [57]. There is some evidence to suggest variations in the ratios of aromatic amino acids and fatty acids synthesized in the vagino-uterine microbiome may have consequences for the functioning or releases of endometrial cells or local immune cells.

14-3-3 and microRNAs

A number of microRNAs show alterations in endometriosis [58], including miR-7, miR-375 and miR-451, all of which regulate the melatonergic pathways and mitochondria functioning. Decreased miR-375 is evident in endometriosis ectopic stromal cells [59]. Decreased miR-375 is linked to raised 14-3-3ζ levels [60] and therefore to 14-3-3ζ-mediated aralkylamine N-acetyltransferase (AANAT) stabilization and NAS synthesis at the start of the melatonergic pathway. Likewise, miR-451 and miR-7 also negatively regulate 14-3-3ζ, with a downregulation of these miRNAs evident in endometriosis and endometriosis-associated ovarian cancers [61, 62]. Such alterations in miRNA-driven changes in 14-3-3ζ-mediated melatonergic pathway initiation may also link to the data showing ectopic endometrial stromal invasion in endometriosis is 14-3-3ζ dependent [63]. This suggests that these miRNAs have a role in co-ordinating the initiation of the melatonergic pathways, and therefore NAS synthesis and associated TrkB activation, with the proliferation and invasion in endometriosis, possibly priming the transition to ovarian cancers.

Low Body Mass Index and Adipocytes

Women with endometriosis have a lower body mass index (BMI) and body fat. A preclinical model suggests that this

may be partly mediated by miR-let 7b and miR-342-3p, which alter fat metabolism and drive down adipocyte stem cell levels, thereby readily overlapping with wider endometriosis symptomatology [64]. Transfected primary adipocytes from women with endometriosis, vs healthy controls, led to significant metabolic changes in this murine model, including in mRNA levels of peroxisome proliferator-activated receptor (PPAR)-γ, leptin, adiponectin, IL-6, and hormone-sensitive lipase (HSL), as well as decreased adipocyte stem cell levels [64]. Such data suggests a close association of low BMI and endometriosis pathophysiology, with a mediating role for miR-let 7b and miR-342-3p [64].

In association with this decreased BMI and lower levels of adipocytes, a decrease in serum and peritoneal fluid adiponectin is evident in endometriosis [65], with adiponectin, via its receptors, decreasing the proliferation of endometrial cells [66]. The decrease in adiponectin mRNA, like IL-6 and HSL mRNA, can be mediated by miR-let 7b, with miR-342-3p increasing leptin. Leptin is generally increased in endometriosis, both in the serum and endometrium, with the down-regulation of leptin associated with improved symptomatology [64, 66]. Adipocyte changes may be driven by circulating miRNAs, especially exosomal miR-let 7b and miR-342-3p [64]. Such wider metabolic changes in endometriosis have led to its classification as a systemic disorder [67], although if driven by endometrial tissue-derived exosomal miRNAs, wider alterations in other tissues and organs would be expected.

Estrogen and Estrogen Receptors (ERα, ERβ)

Endometriosis is usually defined as an estrogen-dependent condition, with treatment aimed at lowering estrogen effects, often at the further expense of decreases in fertility. However, SNPs in ERα are not risk factors for endometriosis, although ERα SNPs do modulate stage transition in endometriosis [68], suggesting a role for ERα in the pathophysiology, but not the pathogenesis of endometriosis. Notably, melatonin inhibits the ERα [69], suggesting that melatonin inhibition in endometriosis may potentiate ERα-driven pathophysiology. ERβ is also increased in endometriosis, where it translocates to mitochondria and drives increases in SOD2 and bcl-2, thereby affording protection against apoptosis [70] as well as heightening mitochondria functioning [71]. Endometriosis risk also correlates with CYP1B1 SNPs [4, 72], with CYP1B1 SNPs correlating with ERα and ERβ levels in regard to endometrial cancer risk [73]. CYP1B1 increases the backward conversion of melatonin to NAS [74], suggesting that the NAS/melatonin ratio may be co-ordinated with CYP1B1, ERα and ERβ, all within mitochondria. This indicates that decreased melatonin by AhR-induced CYP1B1 is co-ordinated with estrogen pathophysiology.

Notably, the relatively heightened levels of estrogen in endometriosis, via ERα, may also significantly inhibit the production of adipocytes from bone marrow [75], as well as triglyceride accumulation in adipocytes [76], either directly or via the regulation of endometrial exosomes. It awaits investigation as to whether mitochondria ERβ levels are increased in endometriosis adipocytes, as occurs in endometrial tissue. Heightened ERβ can significantly upregulate mitochondria functioning, including ATP production [77], as well as decrease levels of ERα and estrogen related receptors (ERR)α and ERRβ, which are also significant mitochondria regulators [78]. This may be of some relevance to the alterations in vitamin A and the decrease in vitamin A metabolites and retinol-binding protein (RBP) in endometriosis, given that ERα, but not ERβ, increases RBP-4 [79]. It requires investigation as to whether the increase in mitochondria ERβ occurs in adipocytes in endometriosis and whether this has any implications for the regulation of the retinoic acids, such as via CYP26. The pathophysiological changes occurring in endometriosis are summarized in Figure 1.

It still awaits clarification as to the mechanisms underlying adipocyte changes in endometriosis. A number of mechanisms are possible, including: exosome release of miRNAs that drive alterations in in adipocytes [64]; heightened levels of estrogen effects at the ERα initially, before a rise in mitochondria ERβ, as in endometrial tissue [80]; micro-metastasis of endometrial cells [57]; early developmental and ongoing alterations in a gut-liver-hypothalamus-adipocyte axis [81]. Clearly alterations in mitochondria metabolic regulation are of some importance.

The importance of prenatal factors are indicated at the top left-hand side of the figure. Maternal factors, as well as decreased vitamin A and melatonin contribute to suboptimal placenta functioning and foetal growth. This leads to alterations in the gut-liver-hypothalamus-adipocyte axis, leading to decreased adipogenesis and low BMI, with resultant alterations in exosomal content coupled to decreased adiponectin, with miR-342-3p likely mediating effects partly via increased leptin. Such a collection of changes have direct effects on endometrial cell functioning and the interactions of these cells with immune cells. A putative decrease in butyrate and ongoing decreases in vitamin A and its retinoic acid metabolites,

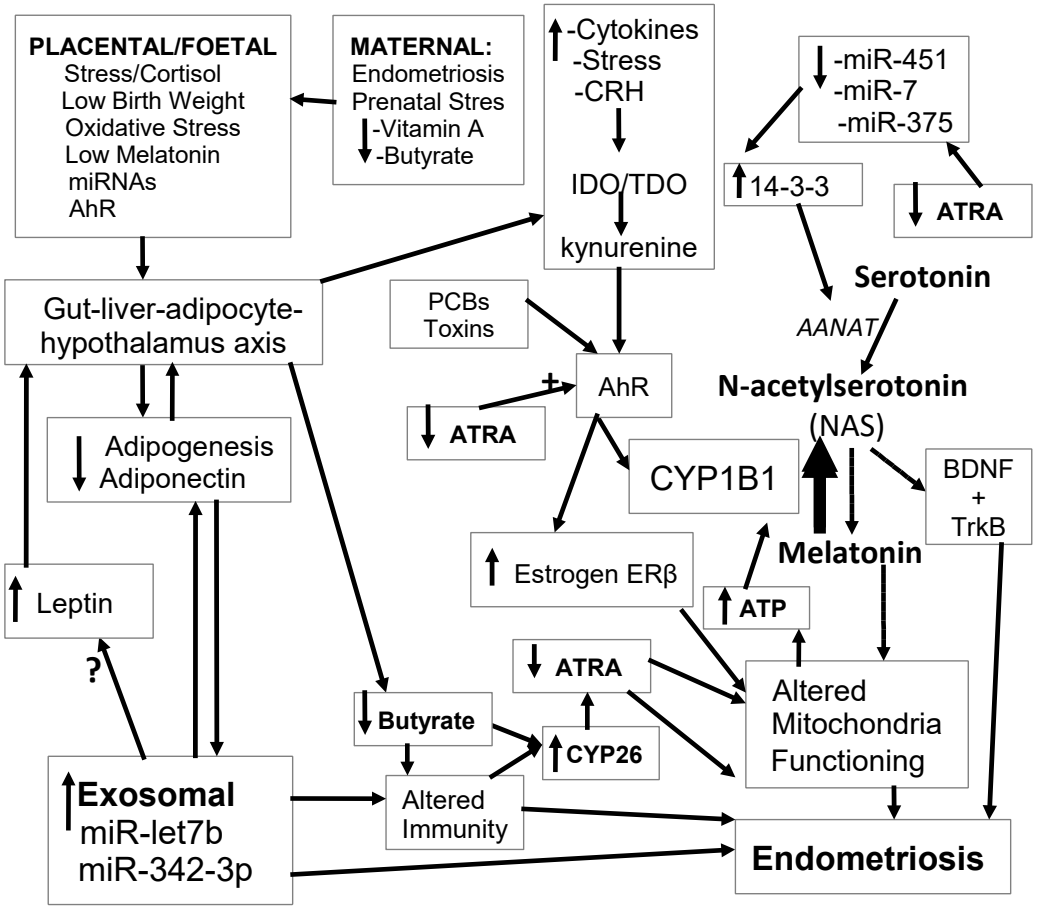

Figure 1: The melatonergic pathways integrate endometriosis pathophysiology.

contribute to endometriosis, in part via decreased melatonin and suboptimal mitochondria functioning. Increased estrogen activation of microchondria ERβ, possibly via increased ATP production, increases the backward conversion of melatonin to NAS, leading to increased BDNF and TrkB activation, contributing to endometriosis. Similar effects arise from exogenous and induced AhR ligands via their upregulation of CYP1B1. Alterations in miRNAs and 14-3-3 proteins in endometriosis will have significant impacts on the melatonergic pathways. The raised CYP26 metabolism of ATRA may be mediated by altered immune-inflammatory activity and lower butyrate. Decreased ATRA has effects at a number of sites, including AhR activity and miRNA regulation. Endometrial lesion cells may also release exosomes that modulate other cells, including adipocytes, but are not shown for clarity. Abbreviations are shown at the end of the article.

Integrating Pathophysiology within Mitochondria

As the data above indicate, there are a plethora of pathophysiological changes in endometriosis. All of these factors may be integrated (see Figure 1).

Although the feminizing and some tumor effects of estrogen are mediated via ERα, the relevant effects of estrogen in endometriosis may be mostly driven by mitochondria-located ERβ [77, 80]. In other cells ERβ forms a complex with glucose regulated protein (Grp)75, which is a mitochondria matrix chaperone. Once within the mitochondria matrix the ERβ-Grp75 complex is stable and drives a significant increase in mitochondria ATP production and alters mitochondria DNA gene expression [77]. There is a dramatic increase in mitochondria-located ERβ in ectopic endometriotic tissue as well as in estrodiol-primed endometriotic cells [77, 80], which show heightened mitochondria bioenergetics coupled to lower ROS, at least partly mediated by raised SOD2

levels [70, 80]. Heightened mitochondria ERβ levels increases migratory activity, which is attenuated by mitochondria respiration inhibition. Such data highlights the importance of mitochondria in the biological underpinnings of endometriosis, including in the changes linked to increased peritoneal estrogen levels.

A consequence of an ERβ-driven rise in mitochondria ATP levels [77] is an ATP-driven backward conversion of melatonin to NAS [82], as can occur with raised levels of mitochondria CYP1B1 [74]. Although NAS and melatonin have many similar effects, NAS is a BDNF mimic via its activation of TrkB, as well as inducing BDNF. As an increase in both TrkB and BDNF are intimate aspects of endometriosis pathophysiology, such increased synthesis and efflux of NAS, at the expense of melatonin, will drive the proliferation evident in endometriosis. This would suggest that an increase in the NAS/melatonin ratio is a significant mediator of the effects of increased estrogen and the dramatic increase in mitochondria ERβ. Endometriosis is associated with an increased risk of migraines [83], which may also be linked to a raised NAS/melatonin ratio [3].

Although vitamin A and retinoic acid metabolites can modulate mitochondria functioning per se, ATRA can not only decrease the raised levels of peritoneal estrogen evident in endometriosis, but can also decrease levels of mitochondria ERβ in endometriotic tissue [45]. Dysregulation of the retinoic acids, including from increased CYP26 [84], may therefore determine the mitochondria and estrogen changes occurring in endometriosis. Such changes are likely to correlate with gut dysbiosis and decreased levels of butyrate production (either from decreased vitamin A, or high circulating pro-inflammatory cytokines, or from pain-associated stress), with correlated consequences arising from a decrease butyrate's immune, mitochondria and melatonin regulatory effects. The loss of butyrate's HDAC inhibition will lower ATRA levels, thereby further attenuating ATRA's inhibition of estrogen and mitochondria ERβ.

Heightened pro- and anti-inflammatory cytokine levels in endometriosis will differentially modulate the levels and activity of different immune cells, including mast cells and macrophages as well as t-cell patterning. Raised peritoneal macrophage levels are evident in endometriosis, with ERβ activation in endometrial stromal cells, leading to M2-like macrophage recruitment [85]. These macrophages are proposed to interact with endometrial nerves in the pathogenesis of an endometriosis preclinical model [86]. As such, increased estrogen and mitochondria ERβ, via M2-like macrophage recruitment, may be seen as an attempt to dampen inflammation, complicated by the changes in endometrial nerves. Autocrine and paracrine effects of melatonin are crucial in shifting macrophages from a M1- to M2-like phenotype [87], suggesting that changes in the melatonergic pathways, including within the mitochondria of macrophages and neighbouring cells, may be important to the nature of the immune responses in endometriosis. This requires investigation. Clearly, alterations in mitochondria functioning are relevant across the host of different cells associated with endometriosis, suggesting dynamic intercellular alterations driven by alterations in mitochondria metabolic regulation.

Heightened pro-inflammatory cytokine levels increase IDO, with oxidative stress and stress-induced corticotropin releasing hormone (CRH) increasing TDO, leading to tryptophan metabolism down the kynurenine pathways and away from serotonin, NAS and melatonin synthesis. Consequently, kynurenine levels are increased, leading to AhR activation. The regulatory effects AhR in many cell types can be lost following its activation by exogenous or induced ligands, such as PCBs and kynurenine. PCBs activation of the AhR increases estrogen and 17β-HSD-7 levels as well as pro-inflammatory cytokines, in a murine model of endometriosis [23]. ATRA can have inhibitory effects on AhR-inductions [88]. As such, exogenous and induced ligands of the AhR are likely to contribute to heightened estrogen and cytokine levels and effects, at least transiently, in endometriosis, which the diminished levels of ATRA fail to inhibit. Estrogen can also potentiate the AhR-induction of CYP1B1, thereby decreasing melatonin synthesis, with increasing CYP1B1 levels being evident over endometriosis stages and in the transition to ovarian tumors [74]. Consequently, the attenuation of ATRA's inhibition of the AhR-induced CYP1B1 contributes to a rise in the NAS/melatonin ratio, and thereby lower melatonin's optimization of mitochondria functioning. Overall, decreased ATRA and an increased NAS/melatonin ratio driven by exogenous and induced AhR ligands in interaction with estrogen contribute to mitochondria dysregulation in endometriosis.

Altered expression levels of a plethora of miRNA can occur in endometriosis, with their patterning changing over the course of lesion progression as part of co-ordinated cellular plasticity responses [58]. The lower levels of miR-7, miR-375 and miR-451 increase 14-3-3ζ [60], thereby stabilizing AANAT for NAS synthesis, leading to TrkB activation and BDNF induction, especially when coupled to increased CYP1B1's backward conversion of melatonin to NAS. Decreases in the retinoic acids may also be relevant to these miRNA effects, given that retinoic acids can dramatically increase miR-375 levels, as shown in adipocytes [89]. As such, decreased retinoic acids will

also contribute to lower melatonin levels via altered miR-375.

The raised stress and pain levels commonly experienced in endometriosis, coupled to increases in pro-inflammatory cytokines, are highly likely to increase gut dysbiosis and permeability. It will be important to determine when this occurs, including any priming role for pre- and post-natal processes and/or whether it is secondary to symptomatic stress and pro-inflammatory cytokine induction. Lower butyrate levels, and its associated HDAC inhibition, drive many of these gut-associated changes, including a host of processes relevant in endometriosis pathophysiology, including mitochondria, immune, melatonin and ATRA regulation [47]. Any role for the uterine microbiome has still to be investigated, including any possibility of a gut-uterine axis that could link alterations in butyrate to cellular processes acting to regulate the uterine microbiome.

Adipocyte regulation in endometriosis will be important to clarify, including roles for endometrial released exosomes [64], decreased ATRA effects, micro-metastasis and wider gut-liver-hypothalamus-adipocyte changes. Notably, melatonin decreases adipocyte stem cell PPAR-γ and adipogenesis via effects in bone marrow-derived mesenchymal stem cells (90-2), suggesting that an increase in melatonin, or NAS [93], will contribute to the decrease in adipocyte levels and adipocyte stem cells in endometriosis. Melatonin also decreases levels of adipocyte-associated fluxes, including leptin and IL-6 [92], suggesting that alterations in both adipogenesis and adipocyte fluxes may be associated with melatonergic pathway modulation that does not necessarily parallel the melatonergic pathway alterations in endometriotic tissue. This will be important to determine, especially regarding etiology and the conceptualization of endometriosis as a systemic metabolic disorder.

Endometrial lesion tissue processes have overlaps with processes important to adipocyte regulation. TrkB is expressed in murine adipocytes, where it can significantly modulate metabolism and weight [94]. As to whether adipocyte TrkB levels and activity are altered in women with endometriosis requires investigation. Also, 14-3-3ζ is crucial to adipogenesis, as a consequence of large interactome with the wide array of factors required in adipocyte differentiation and functioning, as well as its role in the activation of the melatonergic pathways [95]. CYP1B1 inhibition can also decrease adipogenesis in pluripotent stem cells [96], suggesting a role for the NAS/melatonin ratio, possibly around bone marrow cells. Decreased adipogenesis can also be driven by alterations in retinoic acids [97] or decreased gut microbiome-derived butyrate [98], again linking to these interconnected processes, as shown in Figure 1. It is of note that it is variations in mitochondria functioning that determine as to whether bone marrow-derived mesenchymal stem cells differential into bone or adipocytes [99], highlighting the role of alterations in mitochondria functioning at another key site in endometriosis pathophysiology.

Overall, it is clear that much of the pathophysiology of endometriosis is intimately associated with the regulation of mitochondria functioning across a host of cell types and systems. Many of the classical changes in endometriosis are intimately linked to alterations in mitochondria functioning, including changes in estrogen ERβ, adiponectin, melatonin and vitamin A. Such processes are also relevant to the pathoetiology of endometriosis.

Integrating Pathoetiology

Sampson's theory of retrograde menstruation is still widely accepted to reflect core changes driving endometriosis pathoetiology [100]. However, the incidence of retrograde menstruation is far higher than that of endometriosis [101], leading to a revision of Sampson's theory whereby women with endometriosis may show alterations in their immune system, with perhaps a defect in the recognition of endometrial fragments, akin to autoimmune disorders [102].

More recent work has led to the proposal of a set of genetic and epigenetic changes, perhaps linked to the early pre- and post-natal period [103]. Notably, some endometriosis risk factors are strongly associated with early developmental processes, including SNPs in the AhR and CYP1B1. Likewise factors associated with endometriosis pathophysiology, such as miR-451, vitamin A and the melatonergic pathways have crucial roles in the regulation of placenta and foetal development [52]. It is also widely accepted that alterations in prenatal processes can modulate many postnatal events via changes in the gut and gut microbiome development. As such, there may be scope for perinatal modelling of the etiology of endometriosis, linking to a host of genetic and epigenetic processes [103]. For example, alterations in the gut-liver-hypothalamus-adipocyte may modulate the levels of melatonin and retinoic acids that then act to decrease the differentiation of bone marrow-derived mesenchymal stem cells into adipocytes. Presumably, the low BMI evident in endometriosis can predate endometrial symptomatology, suggesting that early developmental processes underpinning changes in fat regulation may be intimately linked to endometriosis pathoetiology and

pathophysiology. Decreased adipogenesis may act to prime endometrial cells, via a decrease in adiponectin, including in regulation of the NAS/melatonin ratio. Further research across these disparate arrays of research may indicate how relevant such early developmentally shaped processes are to the pathoetiology of endometriosis. This is a redefinition of endometriosis from a gynaecological condition to a developmental systemic disorder.

An early developmentally-driven alteration in adipocyte regulation indicates a role for altered adipocyte fluxes and exosomes in endometriosis, which then act to regulate the maturing uterus, either directly or via alterations in uterine-interacting immune cells. Or this could suggest prenatal epiphenomenal alterations in fat and uterine tissue development. A broad body of data shows adipocyte exosomes to modulate a plethora or other tissues, including in the etiology of breast cancer [104]. The alterations in the adipocytes of women with endometriosis would suggest that adipocyte-derived exosomes in endometriosis are distinct and may have differential effects in different tissues, either directly and/or via immune cells [105].

Different exosomal miRNAs can regulate the macrophage phenotype, e.g. miR-let 7 increases an M2-like phenotype (106-7). This would suggest that the proposed role of M2-like macrophages that infiltrate the uterus in high numbers, may be influenced by their interactions with adipocyte-derived exosomes, as well as fluxes and exosomes derived from endometrial cells [64]. Under inflammatory conditions, macrophages and other immune cells would be expected to show an M1-like inflammatory response to eliminate pathogens and inappropriate cells, which then shifts to a debris-clearing M2-like phenotype associated with homeostasis resolution. The attraction and maintained presence of an M2-like macrophage phenotype that fails to eliminate sources of inflammation can contribute to an immune tolerance, as in endometriosis-associated ovarian cancer [108]. The developmental etiology of adipocyte alterations in endometriosis will be important to determine.

An early developmental etiology to endometriosis is supported by longitudinal data from Sweden, showing that low birth weight for gestational age associates with a subsequent endometriosis diagnosis, which the authors interpret as showing a role for prenatal growth restriction in endometriosis pathoetiology [109]. This may be complicated by the genetic links to endometriosis, as women with endometriosis are more likely to have small for gestational age offspring, as well as increased levels of preeclampsia during pregnancy [110]. However, when maternal endometriosis and other prenatal factors were partialed out, the association of low-birth weight and later endometriosis was still significant, indicating a prenatal etiology to endometriosis. The increased endometriosis risk from AhR SNPs [21] may be mediated by changes occurring prenatally, including within the placenta, where the AhR has a regulatory role that can be dramatically altered by exogenous and induced AhR ligands. Given the lower melatonin levels in pregnancies with endometriosis associated conditions, such as preeclampsia, decreased placental melatonin may contribute to the prenatal etiology of endometriosis. As such, key changes in endometriosis pathophysiology may also be important to any prenatal etiology.

Prenatal retinoic acid signalling in crucial to fertility [111]. During the first trimester fetal growth is totally dependent upon endometrial secretions mediated by endometrial stromal cells, including a critical role for glycogen, with infertile women generally having very low glycogen as well as retinoic acid levels. Adipocyte-secreted glycogen controls this glycogen metabolism and secretion in endometrial stromal cells, as well as its foetal uptake [112]. This indicates that maternal endometriosis, in association with low adiponectin, retinoic acid signalling and altered exosome content, will not only modulate fertility, but also foetal development, including in the development of the foetal uterus. As to whether such early, primarily first trimester processes, prime adipocyte and uterine changes relevant to low BMI and endometriosis in the offspring requires investigation.

Other perinatal factors are also associated with an increased risk of endometriosis, including cesarean section, premature birth and formula feeding (vs breastfeeding) [113]. Notably, breastfeeding benefits may be mediated via the regulation of the infant's gut microbiome and the melatonergic pathways [114]. Cesarean section leads to a perturbation of the infant gut microbiota that is partially restored by breastfeeding [115]. As such, perinatal, and perhaps prenatal, endometriosis risk factors may be ameliorated by the regulation of the gut microbiome, including by breastfeeding, highlighting the gut as an important hub upon which risk factors may be interacting in the early developmental pathoetiology of endometriosis.

The induction of endometriosis symptoms in mice leads to alterations in hepatic metabolism [116]. These authors found that inducing endometriosis led to significant alterations in 26 hepatic genes, 6 of which are involved in metabolic regulation, with changes linked to increased metabolism and decreased weight gain. Such data suggests that endometriosis symptomatology can also drive the low BMI and associated adipocyte changes,

at least in part via alterations in hepatic metabolic regulation. Such data indicates that local endometrial tissue changes may drive a systemic condition. Notably, hepatic exosomes can significantly modulate adipocyte function [117], whilst the levels of adiponectin release by adipocytes influences the levels and contents of exosomes [118], suggesting that the decreased adipogenesis and adiponectin levels in endometriosis will be associated with an array of alterations in the levels and contents of exosomes, which may interact with adipocyte regulating factors in hepatic exosomes.

As melatonin has inhibitory effects on estrogen ERα signalling, a feedback inhibition of the melatonergic pathways by estrogen may be a core aspect of the local pathoetiological underpinnings of endometriosis. This may be achieved by a number of means, including the potentiation of the AhR's induction of mitochondria CYP1B1, as is evident in cancer cells, and/or an upregulation of ATP production via mitochondria ERβ [82]. As such, dysregulation in the mutual antagonistic interactions of estrogen and local melatonin production may be an occluded aspect of pathoetiology and pathophysiology.

Overall, the pathoetiology of endometriosis has still to reach an accepted consensus. A growing literature suggests that the prenatal environment is important. As to whether low BMI is upstream or downstream of endometrial changes or concurrently regulated by systemic processes is the subject of current research. A growing body of data suggests that prenatal factors are important mediators of endometriosis, with significant impacts on the melatonergic and vitamin A/retinoic acid pathways, with consequences for the association of endometriosis with a number of cancers.

Treatment implications

The conceptualization of endometriosis as an estrogen-dependent disease has led to treatments that have primarily focussed on the inhibition of estrogen and/or an increase in progesterone. Consequently, combination hormonal contraceptives and progestins are the first-line treatments for endometriosis. These usually have some efficacy in pain management and are reasonably well tolerated. Outwith the long-term side-effects of such treatments, many women experience no, or only partial, improvement in pain. Discontinuation usually leads to symptom recurrence. A number of newer pharmaceuticals, again centred on estrogen-dependent aspect of endometriosis, have shown promise, including GnRH antagonists and CYP19A1/aromatase inhibitors, reviewed in [119]. It should be noted that GnRH is also a significant regulator of the gut, enteric nervous system, IgM responses and gastrointestinal motility, which may all be affected by GnRH antagonism [120].

As indicated by the complexity of factors relevant to the pathoetiology and pathophysiology of endometriosis, a number of novel treatments emerge.

Melatonin 10 mg/day, versus placebo, has shown efficacy in a phase-II clinical trial [121]. Melatonin lowered daily pain and dysmenorrhea by 40%, whilst also significantly reducing BDNF levels (independent of pain regulation). Melatonin also improved sleep quality and reduced analgesic use by 80% (S121), as well as having anti-estrogenic effects. As melatonin lowers the inflammatory content of adipocyte-derived exosomes, there are less detrimental effects of these exosomes in other organs, including the liver [122]. This suggests that melatonin will alleviate any symptomatology associated with adipocyte (and possibly endometrial) exosomes in other organs and immune cells. Given its high safety profile, the use of melatonin, alone or adjunctive, is an immediately practicable treatment that may be intimately linked to endometriosis pathophysiology, as indicated above.

For women with endometriosis, there is a heightened risk of poor pregnancy outcomes, including an increased risk of preeclampsia, neonatal death, still-birth and small for gestational age [110]. Melatonin treatment during pregnancy is likely to lower the likelihood of such poor pregnancy outcomes [123].

Vitamin A and its retinoic acid metabolites, especially ATRA, significantly modulate endometriosis pathophysiology. Diet and supplements to increase vitamin A are likely to afford some benefits and may also improve any concurrent gut dysbiosis and gut permeability, as well as increase the availability of local melatonin [48].

Butyrate supplementation, as with sodium butyrate, is also likely to improve any gut dysbiosis and gut permeability. Butyrate, as a HDAC inhibitor, would be expected to increase the availability of ATRA [47], and therefore increase the benefits of ATRA on mitochondria functioning, possibly via CYP26 inhibition [49,] as well as inducing the melatonergic pathways [48]. Butyrate, like melatonin, will also dampen any heightened immune-inflammatory activity, including that induced by stress-induced gut dysbiosis.

Given the proposed role of ERβ as an important driver of mitochondria alterations in endometriosis [77, 80], the modulation of estrogen effects at the ERβ is a significant

treatment target. As the increase in mitochondria ERβ is associated with higher levels of estrogen availability, increasing ATRA, including via butyrate's HDAC inhibition, will not only decrease peritoneal estrogen levels, but the raised mitochondria ERβ levels in endometriotic tissue [45].

Future Research

Treatment Orientated

What are the processes that are altered in the benefits of melatonin treatment of endometriosis? Are there benefits mediated via changes in oxidative stress, immune-inflammatory activity, gut permeability, exosomes and/or more directly on endometrial tissue? Research similarly aimed at exploring these processes will also be relevant in regard to butyrate and vitamin A.

Is there an increase in the NAS/melatonin ratio within mitochondria in endometrial tissue? If so, do increases in mitochondria CYP1B1 or ATP production or some other means mediate such ratio changes. Such research would provide a significant focal treatment target.

Are there changes in gut SCFAs in endometriosis, especially in butyrate level? If so, is this due to a decrease in its levels of production or its uptake over intestinal epithelial cells? Do stress and increased pro-inflammatory cytokines drive changes in gut dysbiosis secondary to endometriosis or is gut dysbiosis and a decrease in circulating butyrate causal to some of the mitochondria changes occurring in endometrial tissue and immune responses? Is gut dysbiosis and decreased butyrate production secondary to lower levels of vitamin A.

Pathophysiology Orientated

It will be important to determine as to whether ATRA modulates AhR-mediated increase in mitochondria CYP1B1 in different endometriosis stages and in the tumor transition, whilst exploring any impact of this on the NAS/melatonin ratio. Similarly, as to the impact of the dramatic increase in mitochondria ERβ on the NAS/melatonin ratio.

It requires determination as to whether the ATRA catabolizing enzymes, CYP26A1 and CYP26A2, are increased in endometriotic tissue.

It requires investigation as to whether the increase in mitochondria ERβ evident in endometrial tissue, also occurs in adipocytes and whether the mitochondria ERβ increase has any implications for the regulation of the retinoic acids, such as via CYP26 regulation.

As well as miR-7, miR-375 and miR-451 regulation of 14-3-3ζ and the melatonergic pathways, it is highly likely that the wide array of dynamic interactions highlighted above are intimately associated with wider alterations in co-ordinated miRNA expression. These will be important to determine, including as to the role of core mitochondria processes in co-ordinating such changes.

Within a conceptualization of endometriosis having a prenatal origin, it will be important to determine alterations in maternal, placenta and foetal fluids as to changes in the many factors highlighted throughout this article, including ATRA, NAS/melatonin, and miRNAs, as well as maternal butyrate circulatory levels and placental 11β-HSD2. Given the higher levels of stress that can be experienced by women with endometriosis, heightened levels of stress and pro-inflammatory cytokines in pregnancy occur, with many of these effects mediated via placental 11β-HSD2 regulation. HDAC inhibition, including from maternal microbiome-derived butyrate, may prevent the effects of cortisol or IL-1β, which decrease placental 11β-HSD2, and therefore the effects of stress in the placenta and foetus [124]. Such prenatal processes will be important to determine.

As AhR SNPs are a susceptibility factor for endometriosis [21], it requires investigation as whether this increased risk is mediated via prenatal factors, including maternal cigarette smoking, which is also an endometriosis risk factor [125], as well as other exogenous and induced AhR ligands, such as factors increasing kynurenine and associated decreases in the melatonergic pathways. A prenatal etiology means that many of the genetic endometriosis risk factors are not necessarily mediating their increased risk effects in endometrial tissue.

Foetal uterus development is highly variable, as measured by growth parameters [126]. It requires investigation as to whether maternal endometriosis-associated factors, such as decreased vitamin A and the retinoic acids or adiponectin [112], have any priming impact on the development of the foetal uterus. This could link foetal uterus development with retinoic acids' modulation of fertility.

The prenatal and early developmental factors acting on adipogenesis will be important to determine. Such data should give a clearer role as to the influence of low BMI in the pathoetiology of endometriosis.

Conclusions

The pathoetiology and pathophysiology of endometriosis is clearly complex and involves a number of factors and processes over the course of development. Clearly most of the factors and processes associated with endometriosis have an impact on mitochondria functioning in a number of different cells, with this underpinning the changes in miRNAs expressed as well as their presence in exosomes. The processes underpinning low BMI and its association with changes in endometrial cells seems crucial to the conceptualization and treatment of endometriosis. There is a growing consensus that maternal and prenatal factors are important drivers of endometriosis, with significant changes in mitochondria functioning mediated by alterations in melatonergic and vitamin A/retinoic acid pathways regulation, both prenatally and subsequently. Changes in such processes clearly have implications for understanding, and preventing, the association of endometriosis with a number of cancers.

Conflict of interest: Author states no conflict of interest

List of abbreviations

AANAT aralkylamine N-acetyltransferase
AhR aryl hydrocarbon receptor
ATRA all-trans retinoic acid
BDNF brain-derived neurotrophic factor
BMI body mass index
CRH corticotropin releasing hormone
CYP cytochrome P 450
ER estrogen receptor
GnRH gonadotropin-releasing hormone
GRP glucose regulated protein
HDAC histone deacetylase
HSD hydroxysteroid dehydrogenase
HSL hormone-sensitive lipase
IDO indoleamine 2,3-dioxygenase
Ig immunoglobulin
IL interleukin
miR microRNA
NAS N-acetylserotonin
NLRP3 Nod-like receptor family pyrin domain containing inflammasome
O&NS oxidative and nitrosative stress
PCBs polychlorinated biphenyls
PPAR peroxisome proliferator-activated receptor
RBP retinol-binding protein
SCFA short-chain fatty acids
SNP single nucleotide polymorphism
SOD superoxide dismutase
TCDD 2,3,7,8-tetrachlorodibenzo-p-dioxin
TDO tryptophan 2,3-dioxygenase
TGF transforming growth factor
Th T helper
Treg regulatory t cell
TrkB tyrosine kinase receptor-B

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