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REVIEW ARTICLE

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Cancer driver mutations in endometriosis: Variations on the major theme of fibrogenesis

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Abstract

Background: One recent study reports cancer driver mutations in deep endometriosis, but its biological/clinical significance remains unclear. Since the natural history of endometriosis is essentially gradual progression toward fibrosis, it is thus hypothesized that the six driver genes reported to be mutated in endometriosis (the RP set) may play important roles in fibrogenesis but not necessarily malignant transformation.

Methods: Extensive PubMed search to see whether RP and another set of driver genes not yet reported (NR) to be mutated in endometriosis have any roles in fibrogenesis. All studies reporting on the role of fibrogenesis of the genes in both RP and NR sets were retrieved and evaluated in this review.

Results: All six RP genes were involved in various aspects of fibrogenesis as compared with only three NR genes. These nine genes can be anchored in networks linking with their upstream and downstream genes that are known to be aberrantly expressed in endometriosis, piecing together seemingly unrelated findings.

Conclusions: Given that somatic driver mutations can and do occur frequently in physiologically normal tissues, it is argued that these mutations in endometriosis are not necessarily synonymous with malignancy or premalignancy, but the result of enormous pressure for fibrogenesis.

KEYWORDS

cancer driver mutation, endometriosis, fibrogenesis, natural history, repeated tissue injury and repair

1 | INTRODUCTION

Endometriosis, defined to be the deposition and growth of endometrial-like tissues outside of uterine cavity, is a benign and a major contributor to pelvic pain and subfertility affecting 6%-10% of women of reproductive age. Despite extensive research, our knowledge on its etiology, pathogenesis and pathophysiology is still fragmentary. Consequently, its effective treatment still remains a challenge.[1] So far the quest for novel nonhormonal therapeutics has not been successful,[2] and there is no single biomarker that has unequivocally been shown to be clinically useful in diagnosing endometriosis.[3-5]

Given its high prevalence, its negative impact on quality of life in afflicted women,[6,7] and its heavy socioeconomic burden,[8-10] there has been an ever burgeoning interest in finding its pathogenesis, pathophysiology, and its optimal management, as evidenced by the exponential growth in the number of articles on endometriosis.[2] It is well accepted that endometriosis is first and foremost

an estrogen-dependent disease, characterized by the estrogen-dependent growth and maintenance of ectopic endometrium and the increased local production of estrogens.[11] It is also considered as an inflammatory condition, featuring increased production of proinflammatory cytokines and chemokines.[11] Recent evidence is accumulating that it is also a procoagulant disease.[12,13]

It has been well-recognized that endometriosis sometimes behaves like a tumor[14] and that it exhibits many features reminiscent of malignancy, such as invasion,[15] neoangiogenesis,[16] and recurrence.[17] As with most neoplasms, which are monoclonal in origin,[18,19] each focus of endometriotic lesions is also monoclonal.[20,21] Similar to cancers,[22] endometriosis also exhibits various epigenetic aberrations.[23] These similarities prompted numerous studies in search of germline mutations or polymorphisms that predispose women to endometriosis or of lesion-bearing mutations or genomic aberrations that can facilitate their malignant potential. Cytogenetic studies demonstrate that there are aberrant somatic genetic alterations, such as loss of heterozygosity (LOH),[24] chromosome aneuploidy,[25-27] and copy number changes,[28-31] which are also hallmarks of cancer,[22,32] even though earlier such attempts found nothing.[33,34] The endeavor to search for genetic predisposing variants all started in the 1990s,[35,36] and took a full swing in the era of genome-wide association studies (GWASs) when high-throughput genotyping methods became available and more affordable.[37,38] With the demand for larger sample sizes with detailed phenotypic and clinical information and thus more resources, the GWAS advocates promise to provide new insights into disease risk, classification, and comorbidity.[39]

Although endometriotic lesions can be found throughout the abdominal-pelvic peritoneum and visceral organs, there are three major subtypes of endometriosis based primarily on their anatomical locations: ovarian endometrioma (OMA) which is reported to be the most common,[40,41] superficial peritoneal endometriosis (SPE), and deep endometriosis (DE).[42] While all subtypes of endometriosis are benign, patients with OMA are well-documented to have elevated risk of developing two particular histotypes of ovarian carcinomas—the endometrioid and the clear cell carcinoma,[43,44] although the magnitude of risk is rather moderate.[45] Given the neoplastic potential of OMA, a slew of studies have been published on the expression and genomic alteration of ARID1A in endometriotic lesions[46-49] following the heels of the report that the gene is frequently mutated in endometriosis-associated ovarian carcinomas.[50]

In contrast, extraovarian DE lesions have not been reported to transform into malignancy. Consequently, it came as a complete surprise when a recent high-profile study reports that the majority (79%) of DE lesions harbor somatic mutations and a sizeable portion of them (26%) contain known cancer driver mutations at ARID1A, PIK3CA, KRAS, or PPP2R1A in the epithelial component.[51]

In contrast to those genomic alterations termed "passenger" mutations,[52] "driver" mutations are implicated in pathways that are critical to the propensity of tumor cells for growth, survival, and metastasis.[53] As such, driver mutations are supposedly rare in benign conditions such as endometriosis, but nonetheless are present in premalignancy and most frequent in metastatic cancer or those with a metastatic potential.[53] While the authors of the driver mutation article were cautious by not sounding any alarm, the heightened vigilance, though guarded and veiled, expressed in the article is nonetheless unmistakable: "cancer-associated mutations" of "driver genes" occur in DE, and "should a more complete genomic or epigenomic analysis be applied, additional drive mutations may be uncovered".[51]

Granted, the paucity of report that DE lesions can be transformed into malignancy may be simply attributable to the rarity or to the lack of attention to this issue. Indeed, other fibrotic diseases, such as cirrhosis, have been reported to have increased potential for malignant transformation.[54] Since the identification of tumor-specific mutations in endometriosis has enormous potential to transform cancer diagnostics, monitoring, and screening if validated, there is a pressing need to evaluate the significance of the reported cancer driver mutations in endometriosis.

Similar to Darwinian evolution, all cells in endometriotic lesions are under selection pressure. Cell clones with driver mutations must have some distinctively selective advantages over those without. As one single most powerful driving force in shaping the natural history of lesions is to progress to fibrosis through ReTIAR, it can be hypothesized that these driver mutations in endometriosis may have more to do with fibrogenesis than from tumorigenesis.

In this article, after providing a brief overview on the natural history of endometriotic lesions, I shall provide an overview on the driver mutations in endometriosis and try to address the following questions from the vista of lesional natural history: What kind of role, if any, do these genes play in fibrogenesis? Do endometriotic lesions harboring these driver mutations truly drive neoplastic transformation? Do patients with DE have an increased risk of developing into cancer? Why these mutations are seen mostly in endometriotic epithelial cells as opposed to the stromal counterpart? What clinical implications, if any, does the finding of drive mutations in lesions have? Can driver mutations in endometriotic lesions reported thus far tell us anything about or shed new light into the pathophysiology of endometriosis?

As the major focus of this review is strictly on somatic cancer driver mutations in endometriotic lesions, I shall not touch upon germline mutations, genetic polymorphisms, genomic alterations, copy number changes, or passenger mutations. The driver genes reviewed here are comprised of two sets: the RP set, which includes TP53, PTEN, ARID1A, PIK3CA, KRAS, and PPP2R1A that have been *reported* to be mutated in endometriosis, and the NR set, which includes ALK, BRAF, CDKN2A, FGFR3, GNAQ, NF1, NF2, NOTCH1, and NRAS, that have *not* been *reported* to be mutated in endometriosis. All genes in the NR set were listed in a recent review article on driver mutations in benign diseases,[53] and they were chosen mainly as a contrast without any prejudice. If the hypothesis is true, then we should expect to see the higher proportion of genes in the RP set than that from the NR set to be documented to play fibrogenic roles, or vice versa. All these genes and their related proteins, along with their upstream regulators and downstream target genes, will be reviewed for their possible roles in endometriosis and fibrogenesis.

2 | METHODS

The PubMed database was searched for all original and review articles published in English until July 18, 2017. Search terms included 'mutation and endometriosis', 'genomic alteration and endometriosis', 'aneuploidy and endometriosis', 'p53 and endometriosis', 'PTEN and endometriosis', 'ARID1A and endometriosis', 'PIK3CA and endometriosis', 'KRAS and endometriosis', 'protein phosphatase 2A and endometriosis', 'PI3K and endometriosis', 'anaplastic lymphoma kinase and endometriosis', 'BRAF and endometriosis', 'CDKN2A and endometriosis', 'p16 and endometriosis', 'FGFR3 and endometriosis', 'GNAQ and endometriosis', 'PTEN and endometriosis', 'NF1 and endometriosis', 'NF2 and endometriosis', 'NOTCH1 and endometriosis', 'NRAS and endometriosis', 'p53 and fibrosis', 'PTEN and fibrosis', 'ARID1A and fibrosis', 'PIK3CA and fibrosis', 'KRAS and fibrosis', 'PPP2R1A and fibrosis', 'protein phosphatase 2A and fibrosis', 'anaplastic lymphoma kinase and fibrosis', 'BRAF and fibrosis', 'CDKN2A and fibrosis', 'p16 and fibrosis', 'FGFR3 and fibrosis', 'GNAQ and fibrosis', 'NF1 and fibrosis', 'NF2 and fibrosis', 'NOTCH1 and fibrosis', 'NRAS and fibrosis', and 'oxidative stress and endometriosis'. The resultantly retrieved articles were reviewed and manually curated, and the gene/protein was considered to be of relevance and included when there was a least one article presented any mechanistic link between the gene/protein of interest and fibrosis.

Fisher's exact test was used to evaluate the statistical significance when comparing the proportions between two groups. Wilcoxon's test was used when comparing the distributions of continuous variables between two groups. *P* values of <0.05 were considered statistically significant. All computations were made with R 3.4.1.[55]

3 | A PRIMER ON THE NATURAL HISTORY OF ENDOMETRIOSIS

While the pathogenesis of endometriosis is still unclear, recent research has provided sufficient details of the natural history of endometriotic lesions. One single defining hallmark of endometriotic lesions is their cyclic bleeding and subsequent tissue repair, just like the eutopic endometrium.[56] Because of bleeding—an indication for tissue injury, platelets are involved and indeed have recently been shown to play important roles in the development of endometriosis.[57] In particular, platelet-derived TGF-β1 drives smooth muscle metaplasia (SMM) and fibrosis through the induction of epithelial-mesenchymal transition (EMT) and fibroblast-to-myofibroblast transdifferentiation (FMT) in endometriotic lesions.[13] Activated platelets impair natural killer cell reactivity and function in endometriosis through multiple mechanisms.[58,59] They also secrete many bioactive factors, including thromboxane A2 (TXA_2), which may also act as a neutrophin, leading to hyperinnervation within or surround endometriotic lesions.[60] Moreover, platelets may also induce epigenetic changes, facilitating the gradual but progressive development of endometriosis, leading ultimately to tissue fibrosis.[61] Both animal and human data lend support for the notion that endometriotic lesions are fundamentally wounds undergoing repeated tissue injury and repair (ReTIAR).[12,62,63] Similar processes also occur in adenomyosis, due to the shared commonality of cyclic bleeding.[64,65]

Note that this natural history may not be necessarily equivalent to the natural history of endometriosis at the organismic level. Women with identical lesions at the same locations may not display identical symptoms or the same severity. This is primarily due to the difference in genetic background and life history, neuronal wiring and coping strategy since endometriosis-associated pelvic pain involves central sensitization[66,67] and is associated with altered brain chemistry and function in the pain matrix.[68,69] Nonetheless, the lesional natural history should constitute the basis for the natural history of endometriosis at the organismic level.

It has long been regarded that OMA, SPE, and DE are three different disease entities and, as such, may have different pathogenesis and pathophysiology. Indeed, gene profiling studies depict different transcriptional signatures in OMA and non-OMA lesions.[70] However, our histological and immunohistochemistry analyses indicate that both OMA and DE share essentially the same features of ReTIAR, and the two conditions differ only by the extent or thoroughness of EMT, FMT, SMM, and the extent of fibrosis, along with different epigenetic aberrations.[71] It turned out that the key factors responsible for the differences between these two subtypes of endometriosis lie in the difference in the microenvironment that OMA and DE lesions are situated: the proximity to sensory nerve plexuses in DE but not in OMA. Sensory nerve-secreted substance P and calcitonin gene-related peptide (CGRP) accelerate the fibrogenic progression, making DE lesions more fibrotic than OMA lesions[72] (Yan et al, unpublished data).

Based on the above discussion, the natural history of endometriotic lesions can be depicted in Figure 1, which also indicates that fibrogenesis of endometriotic lesions also induces cancer driver mutations.

4 | WHY FIBROGENESIS?

As of writing, there are 24 328 published articles on endometriosis (Accessed on September 25, 2017) that are indexed in PubMed. Hundreds, if not thousands, of genes and proteins have been reported to be aberrantly expressed in endometriosis, and many of them have been shown, by painstaking experimentations and to various degrees, to be involved in many aspects of endometriosis development. Despite these discoveries, there is a real issue as how these seemingly unrelated results can be pieced together to have a whole picture as how endometriotic lesions progress and cause symptoms.

Granted, many, if not all, genes are involved in multiple cellular processes. In endometriosis, for example, tissue factor (TF) was first reported in the context of angiogenesis,[73] but now with the

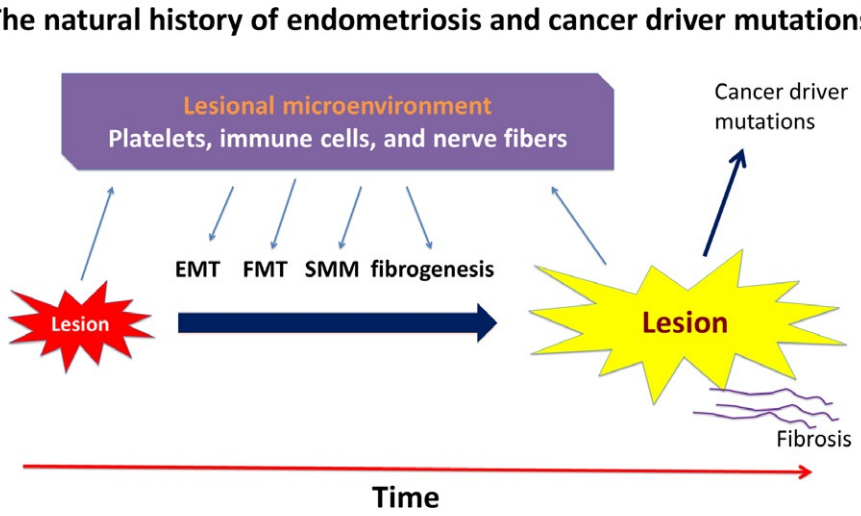

FIGURE 1 The natural history of endometriosis and cancer driver mutations (adapted from Ref. 401). This diagram sketches, in broad strokes, the progression of endometriotic lesions, which interact with various players in their microenvironment, through epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), and smooth muscle metaplasia (SMM), leading ultimately to fibrosis. In addition, it depicts cancer driver mutations are likely induced by the pressure of fibrogenesis of endometriosis. EMT, epithelial-mesenchymal transition; FMT, fibroblast-to-myofibroblast transdifferentiation; SMM, smooth muscle metaplasia

elucidation of the role of platelets in particular and coagulation in general in the development of endometriosis,[57,74] there is reason to believe that the major role of TF in endometriosis is the activation of the coagulation, and its role in angiogenesis may well be its sideline job. This can be understood once we understand that TF plays a vital role in the activation of the coagulation pathways.

Through the prism of ReTAIR, it is easy to see that fibrogenesis starts after lesions are initially formed and becomes an integral part of the lesional development, as well as an end result. Thus, fibrogenesis should be a major theme throughout the progression of endometriotic lesions, and cancer driver mutations are likely to be variations on the theme.

By definition, fibrogenesis is a pathological process characterized by excessive production and deposition of extracellular matrix (ECM) products in response to uncontrolled tissue repair.[75] Despite a wide diversity in different fibrotic diseases, all of them share several commonalities, ie, parenchyma injury, accumulation of fibrillar ECM, accumulation of fibroblasts, rarefication of the microvasculature, and a mononuclear infiltrate.[75] In endometriotic lesions, similar features can be seen: injury to glandular epithelium due to cyclic bleeding, accumulation (due to EMT and perhaps also proliferation) and activation of fibroblasts (due to FMT), reduced vascularity in DE,[71] and infiltration of macrophages and dendritic cells.[76,77]

In addition, endometriotic lesions are very similar to organs that undergo fibrogenesis. In fact, they behave very much like an organ, having all the physiological processes that a normal organ does, such as angiogenesis, lymphoangenesis, and neurogenesis,[78] which provide means for lesions to access to nutrients and oxygen, waste disposal, and communication with the outside just like an organ.

Further thinking along this line would reveal that one can weave many, if not all, known results together to come up with a more or less complete tapestry on the physiopathology of endometriosis. Indeed, without a framework, many of us would be groping, often seeing a leaf very clearly but having no idea as what the forest likes like. Once we have an even skeletal framework, we can piece together all the rest of puzzles more quickly. More importantly, it can help us understand why there are such aberrations and guide us to discover new things.

5 | MUTATIONS OF CANCER DRIVER GENES IN ENDOMETRIOSIS AND THEIR POSSIBLE ROLES IN FIBROGENESIS

The numbers of articles retrieved from the search of PubMed using different search phrases are listed in Table 1. The average number of papers that were found to be more or less related with fibrosis for the genes in the RP is 232.2 (±259.4), which is 7.2 folds higher than that for the genes in the NR set (32.3 ± 34.5). This difference is nearly statistically significant ($P = 0.065$, by Wilcoxon's test), indicating that the genes/proteins in the RP set had an enrichment of articles on their link with fibrosis. Consistent with the division of the RP and NR sets, the genes/proteins in the RP set had significantly more articles that are related with endometriosis (58.8 ± 44.4 vs 6.1 ± 8.2; $P = 0.006$).

5.1 | Mutations in ARID1A, PIK3CA, KRAS, and PPP2R1A in endometriosis and their roles in fibrogenesis

So far six cancer driver genes, TP53, PTEN, ARID1A, PIK3CA, KRAS, and PPP2R1A have ever been reported to be mutated in endometriosis. In particular, TP53, PTEN, and ARID1A mutations are inactivating, and that of PIK3CA, KRAS, and PPP2R1A are of activating

TABLE 1 Number of articles retrieved from PubMed on the cancer driver genes and their roles in fibrogenesis and endometriosis (accessed on July 18, 2017)

Gene/protein name	Possible roles in fibrosis	Aberration in endometriosis
p53	619	128
PTEN	165	86
ARID1A	2	66
PI3K	493	37
KRAS	59	33
Protein phosphatase 2A	55	3
Anaplastic lymphoma kinase	16	0
BRAF	38	13
CDKN2A	43	14
p16	110	24
FGFR3	9	1
GNAQ	1	0
NF1	30	2
NF2	7	0
NOTCH1	67	6
NRAS	2	1

in nature.[51] Before attempting to understand why and how these mutations occur, it may be helpful to evaluate their possible roles in fibrogenesis, which is the end result of the natural history of endometriosis.

5.1.1 | TP53

Tumor protein p53 (TP53), also known as p53, is a well-recognized tumor suppressor gene (TSG) that regulates cellular proliferation and apoptosis.[79] It is hailed as "the guardian of the genome" due to its role in conserving stability by preventing genome mutation.[80] It is frequently mutated in various cancers,[81] especially in serous endometrial carcinomas (89% of patients) and serous ovarian carcinomas (95%).[82]

Since the first report of TP53 mutation in an endometriotic lesion (out of 14) adjacent to ovarian carcinoma in 1998,[83] TP53 loss was soon reported,[84] followed by a report of LOH.[85] Later studies reported somewhat mixed results. Several studies reported no LOH at the TP53 locus in OMA (0/16),[86] no hot spot mutation at TP53 in endometriosis (0/23),[87] no mutation but only focal expression of TP53,[88] and no mutation in endometriotic lesions associated with ovarian cancer (0/12).[89] However, since the mutation rate is presumably low, a large sample size is typically needed to detect it. For example, even if the mutation rate is 10%, the probability of observing none among 16 and 23 samples would be 0.19 and 0.09, respectively, certainly not a small-probability event. Therefore, the negative reports that evaluated just small or moderate samples of endometriotic lesions should be viewed as suggestive, in need for independent confirmation. Assuming a mutation rate of 5% (or 10%), one needs to examine at least 59 (or 29) samples in order to have the 95% probability of observing at least one mutation in the samples. A mutation rate lower than 5% would require even more samples to evaluate.

A recent study demonstrated that conditional deletion of p53 coupled with the activating K-ras mutation led to development of endometrioid ovarian carcinosarcomas.[90] In addition, the combined mutations resulted in simple endometrioid glandular morphology and peritoneal endometriotic lesions as early as 4 weeks after AdCre injection through the ovarian,[90] indicating that TP53 loss, in conjunction with KRAS activation, may transform OMA into malignancy.

The published results on TP53 expression in endometriotic lesions are also conflicting. TP53 overexpression in the epithelial component of lesions,[88,91] in atypical endometriosis,[92] and in OMA [93] has been reported, but this is at direct odds with a later gene profiling study that reported its downregulation.[94] Another study found the TP53 expression to be the highest in OMA, followed by colorectal endometriosis (presumably DE) and then SPE—all in the *epithelial*, but not stromal, component.[95] One study found no difference in TP53 expression between ectopic and control endometrium,[96] the others found no TP53 expression in endometriosis,[97] OMA,[98,99] and DE.[100] One recent study reported downregulation of TP53 in OMA, which is concomitant with increased expression of genes involved in autophagy and elevated protein expression of heme oxygenase-1 (HO-1), a sign of oxidative stress.[101]

Based on the findings published so far and reviewed above, there are reasons to believe that TP53 is likely to be downregulated or even silenced in endometriotic lesions. As such, especially considering the central role of TP53 in tissue repair[102] and the risk of malignant transformation of OMA, the possibility of inactivating TP53 mutation or epigenetic silencing in endometriosis cannot be ruled out. This leaves out the question as what biological consequence, if any, it would entail if TP53 is inactive.

Depending on cell/tissue type and disease models, TP53 has been reported to have different roles in the pathogenesis of fibrosis. The deletion of p53 in proximal tubule cells is reported to prevent interstitial fibrogenesis after acute kidney injury (AKI) in mice.[103] However, other studies reported that p53 inhibition/knockout promoted renal fibrosis.[104,105]

One important mechanism that TP53 loss is responsible for fibrogenesis is due to its role in regulating cellular senescence.[106] In responding to DNA damage, oncogene activation, hypoxia, and telomere shortening, TP53 becomes transcriptionally activated, leading to cell-cycle arrest, DNA repair, and apoptosis.[107] Yet cellular senescence is simply a stable form of cell-cycle arrest that limits the cellular proliferative potential.[108] Indeed, activation of endogenous p53 in liver cancer induced senescence and tumor regression in mouse.[109] In normal wounds, activated fibroblasts initially proliferate in response to tissue damage and secrete extracellular matrix (ECM) products, then senesce, and are eventually removed from the wounding sites. In pathological conditions such as chronic tissue injury, however, repeated tissue injury, followed by fibroblast proliferation, results in

the production of senescent cells outpacing their removal, leading to persistent inflammation and progressive fibrosis.[110] TP53 deletion in *fibroblasts* is found to diminish senescence and to increase TGF-β1 expression, leading to increased activated fibroblasts, more ECM deposition, diminished immune surveillance, and fibrosis.[110] In a nutshell, the senescence program curtails the fibrogenic response to tissue damage, but TP53 loss impairs this program, exacerbating the fibrogenic response.

Consistent with the potential role of TP53 in fibrogenesis in endometriosis, endometriotic cells are reported to have longer telomeres and higher telomerase expression.[111-113] In addition, miR-125b is found to be critical for FMT and fibrosis, and to promote fibroblast proliferation through suppression of TP53.[114] Remarkably, miR-125b upregulation has been reported in endometriosis.[115,116] Moreover, PPARγ is expressed in normal endometrium[117] but is downregulated in ectopic endometrium.[118,119] This appears to mirror what has been reported in liver fibrogenesis: PPARγ is highly expressed in quiescent hepatic stellate cells (HSCs, ie, fibroblasts) but downregulated in activated HSCs.[120,121] PPARγ promotes cellular senescence in fibroblasts,[122] and PPARγ agonists induce apoptosis and cell-cycle arrest in cancer cells.[123]

In endometriosis, the PPARγ staining levels correlated negatively with the extent of fibrosis,[71] similar to the PPARγ inactivation that has been reported to be involved in fibrosis in various organs.[124-126] In particular, MeCP2-mediated enhancer of zeste homolog 2 (EZH2) activation, trimethylation of histone 3 lysine 27 (H3K27me3) and PPARγ suppression have been reported during myofibroblast activation,[125] and in both OMA and DE lesions PPARγ suppression, EZH2 activation and increased H3K27me3 expression have been reported.[71] In fact, EZH2 is found to induce EMT and thus fibrogenesis in endometriosis, and there are signs to indicate that platelet aggregation in lesions may be responsible for EZH2 activation.[61] Importantly, EZH2 may mediate the repression of GSK-3β and TP53 and promote the activation of the Wnt/β-catenin signaling pathway.[127] The profibrogenic role of the Wnt/β-catenin signaling pathway in endometriosis has recently been reported.[128,129] EZH2 can also suppress Dkk1, a negative regulator of the Wnt/β-catenin signaling, inducing fibrosis.[130] Again, Dkk1 expression is reported to be reduced in endometriosis.[131]

TP53 is recently found to restrict the expression of de novo DNA methyltransferases DNMT3A and DNMT3B while upregulating TET1 and TET2 that promote demethylation.[132] TP53 loss results in augmented overall DNA methylation and increased methylation landscape heterogeneity. Incidentally or not, DNMT3A and DNMT3B are both reported to be elevated in endometriotic lesions.[133,134] In addition, TET1, TET2, and TET3 expression is reported to be decreased.[135]

Taken together, there are reasons to believe that TP53 is downregulated or even inactivated in endometriotic *stromal* cells. This inactivation may be due to inactivating mutation, but could also be attributable to its hypermethylation[136] or transcriptional suppression by, say, miR-125b overexpression. The loss of TP53 may retard the senescence of fibroblasts in endometriotic lesions, facilitating fibrogenesis. This assertion may be bolstered by an integrative analysis of gene expression database that identified TP53 as one of 26 transcription factors involved in the regulatory programs associated with differential gene expression in endometriosis.[137]

Note that inactivating TP53 mutation also has been reported in rheumatoid arthritis, which does not confer increased cancer risk.[138,139] This seems to indicate that TP53 mutations can and do occur in nonmalignant tissues which are not premalignant. Thus, inactivating TP53 mutation alone in lesions may not be equated with premalignancy.

5.1.2 | PTEN

PTEN, or phosphatase and tensin homolog deleted on chromosome 10, is a powerful tumor suppressor through regulation of proliferation and survival and has been dubbed as "a new guardian of the genome".[140] It is the second most frequently mutated gene in human cancers after TP53, but the mutation spectrums of PTEN and TP53 are different.[140] In addition, p53-null mice are viable, develop normally and exhibit spontaneous tumors,[141] but homozygous deletion of Pten is embryonically lethal.[142] It inhibits PI3K/AKT signaling by converting PIP3 to PIP2.[140] Of particular interest to endometriosis is its ability in maintaining genomic stability.[143-145]

In endometriosis, the first attempt to evaluate PTEN mutation yielded negative results,[146] but the other study reported a mutation frequency of 21% (7/34) in OMA.[147] One study found no mutation at PTEN (0/23),[87] but the negative finding may be simply attributable to lack of adequate statistical power due to moderate sample size. Another recent study detected 17 mutations in 32 (53%) rASRM III/IV lesions.[148] PTEN loss and LOH have been reported in endometriosis malignant transformation.[89,147,149] Conditional deletion of Pten is found to induce endometriosis in mouse.[150]

Reduced PTEN expression has been reported in endometriosis.[151-153] 17β-estradiol promotes cell proliferation through activating PI3K/AKT and MAPK/ERK signaling pathways via an NF-κB/PTEN-dependent pathway in endometriotic epithelial cells.[152] IL-8 also is reported to enhance proliferation, reduce apoptosis in endometrial stromal cells through the upregulation of survivin and Bcl-2, inhibition of PTEN and activation of AKT.[154] Consistently, AKT activation has been shown to promote the establishment of endometriosis.[155] PTEN suppression inhibits the proliferation and angiogenesis, increases apoptosis and cell-cycle arrest in endometriotic epithelial cells but forced PTEN expression reverses these changes.[156]

During normal tissue repair, excessive fibroblasts are removed by apoptosis, thus limiting fibrosis.[157] Specifically, fibroblasts transdifferentiate into myofibroblasts in response to injury,[158] as seen also in endometriosis.[62] Myofibroblasts produce and then deposit type I collagen into the provisional wound matrix.[159] They also contract the type I collagen matrix, and, in conjunction with reepithelialization, facilitate wound closure.[157,159] In response to collagen matrix contraction, fibroblasts incorporated into type I collagen matrices undergo apoptosis.[159] The contraction of collagen matrix induces PTEN expression, resulting in reduced AKT activation and subsequent

apoptosis.[160] Conversely, PTEN inactivation augments AKT activity, suppresses the apoptosis of fibroblasts, and enhances their proliferation and invasiveness.[160-163] PTEN loss in renal injury also initiates SMAD3- and TP53-dependent fibrotic response.[164] Overexpression of PTEN reduces fibroblast activation, viability, caspase-3 activity, cell-cycle arrest in the G0/G1 and G2/M phases and suppression of PI3K/AKT and FAK/ERK signaling pathways.[165] PTEN also regulates M2 macrophage polarization through activation of PI3K/AKT/STAT6, with its loss yielding more profibrotic M2 macrophages.[166]

There is a wealth of literature documenting the critical role of PTEN loss in fibrogenesis. In many fibrotic diseases, myofibroblasts have diminished PTEN expression[161] but overexpression of PTEN or its reconstitution results in suppression of AKT and consequent fibrogenesis.[167-169] In many fibrotic diseases, PTEN expression is reduced or simply absent.[170-175] Aberrant PTEN/AKT signaling inactivates FOXO3a, a proapoptotic factor, promoting fibrosis.[176,177] Several putative regulators of PTEN have been reported, including caveolin-1,[178,179] DJ-1,[180] and miR-21.[181-188] Remarkably, lower expression of caveolin-1 has been reported in adenomyosis,[189] and higher expression of DJ-1[153,190] and miR-21[191,192] has been reported in endometriosis as well. Inactivation of FOXO3a by SGK1 and ERβ also has been reported in endometriosis.[193] Fibrosis caused by the PTEN loss has been shown to be critically dependent on CCN2/CTGF,[194,195] which is reported to be upregulated in endometriosis.[62,196,197] Evidence also shows that one mechanism for PTEN loss or silencing is its DNMT1-mediated promoter hypermethylation.[198] Inhibition of EZH2, a histone methyltransferase catalyzing trimethylation of H3K27 and of H3K9 which serve as anchorage points for the recruitment of additional PRC2 proteins, has been shown to attenuate fibrosis through induction of PTEN expression.[199] Interestingly, EZH2, along with its PRC2 partners EED and SUZ12, is found to induce EMT in endometriosis[61] and its expression is elevated in endometriosis, especially in DE lesions that exhibit higher fibrotic content.[71]

In light of the above discussion, it can be concluded that as endometriotic lesions undergo ReTIAR and progress to fibrosis, PTEN expression is reduced or perhaps even silenced, leading to the activation of PI3K/AKT/mTOR and also FAK/ERK signaling pathways, and ultimately to fibrosis. The inactivating PTEN mutation may be simply due to the strong pressure of fibrogenesis.

5.1.3 | ARID1A

ARID1A (the AT-rich interactive domain 1A) encodes the protein BAF250a that participates in forming Switch/Sucrose nonfermentable (SWI/SNF) chromatin remodeling complexes, which are crucial for regulating temporal and spatial gene expression during development.[200] In particular, the SWI/SNF subunit BAF250a has been reported to affect self-renewal and differentiation in many tissues and embryonic stem cells.[201,202] As a TSG, ARID1A is frequently mutated in ovarian clear cell and endometrioid carcinomas as well as in uterine endometrioid carcinomas.[50,203,204] One recent in vitro study reports that ARID1A knockdown is sufficient to initiate neoplastic transformation in conjunction with epigenetic reprogramming in nontumorigenic endometriotic cells.[205]

Complete absence of ARID1A staining has been reported in 15% (3/20) of OMA, 5% (1/22) of DE, but in none of SPE (0/16) lesions and eutopic endometrium samples (0/30).[46] Partial loss of ARID1A staining (ie, in one tissue section some cells are stained positive while others are negative) has been reported to be in 36% (9/25) of rectovaginal DE samples.[48] ARID1A gene expression levels in endometriosis are significantly lower than that of control endometrium, and oxidative stress downregulates ARID1A.[206] Incidentally or not, loss of chromosome 1p36.12, where the ARID1A locus is located, also was reported in both ectopic and eutopic endometrium from a woman with SPE.[31]

Tissue regeneration or repair has been reported to resemble the embryonic developmental process since both processes undergo reorganization and rearrangement of tissue architecture concomitant with distinct transcriptional patterns.[207] Thus, it comes with little surprise that the loss of ARID1A is reported to promote liver and ear hole wound regeneration but its forced expression impairs regeneration in mouse models.[208] More specifically, ARID1A knockdown remodels chromatin through reduced H3K4me2 marks, disengaging the transcriptional access by C/EBPα, which enforces differentiation, and E2F4, which suppresses proliferation and regeneration through cell-cycle reentry.[208] It also reduces the expression of FOXA2,[208] a key transcription factor that regulates cell differentiation and tissue regeneration,[209] and HNF4A, a transcription factor. ARID1A expression is suppressed in regenerating tissues, and genetic deletion of ARID1A enhances tissue repair.[208] Remarkably, ARID1A is suppressed after tissue injury and the enhancement of tissue repair by ARID1A loss is not tissue-specific.[208] ARID1A is reported to play a critical role in modulating epithelial proliferation in endometrium and to be essential for endometrial function during early pregnancy.[210]

As endometriotic lesions are fundamentally wounds undergoing ReTAIR, the loss of ARID1A following cyclic bleeding, especially in the epithelial component, may be more common than previously thought. Chronic inflammation[211,212] and prolonged transcriptional suppression[213,214] could lead to promoter hypermethylation and eventually to inactivating mutation at ARID1A when exposed constantly in a hostile microenvironment. Interestingly, LSD1 is reported to be overexpressed in endometriosis, concomitant with reduced H3K4me marks as well.[215,216] In addition, C/EBPα is reported to be epigenetically silenced in endometriotic epithelial cells, which can be reactivated by valproic acid, an HDAC inhibitor.[217] Activation of C/EBPα induces apoptosis and activation of caspase-3 and caspase-7, and its suppression leads to downregulation of PPARγ, p53, Bax, caspase-8, and caspase-10, $p16^{INK4a}$, $p21^{Waf1/Cip1}$, CDK2, and CDK4.[217] FOXA2 is found to be downregulated in endometriosis.[137] Along with TP53, ER-β, Smad3, β-catenin, c-Myc and others, ARID1A regulated FOXA2, HNF4A, and E2F4 are among the 26 transcription factors identified to be involved in the regulatory programs associated with differential gene expression in endometriosis.[137]

In light of the above discussion, there are reasons to believe that AIRD1A is under constant pressure for its suppression in

endometriotic epithelial cells because of ReTIAR. Prolonged transcriptional suppression may lead to epigenetic suppression, which, in some cases, could further lead to its inactivating mutation. Epigenetic suppression through promoter hypermethylation is likely since both de novo and maintenance DNMTs are all upregulated in endometriosis.[133]

5.1.4 | PIK3CA

The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT signaling pathway is one of the most frequently mutated in human cancers.[218]PI3K/AKT pathway is the primary physiological target of PTEN.[219] Somatic alterations in this pathway include mutation and/or amplification of the genes encoding the PI3K catalytic subunits p110α (PIK3CA) and p110β (PIK3CB), the PI3K regulatory subunit p85 (PIK3R1), the PI3K effectors AKT1, AKT2, and PDK1, and the loss of the lipid phosphatases PTEN and INPP4B.[220] PIK3CA uses ATP to phosphorylate phosphatidylinositols and its mutations are the most common genetic alteration of this pathway, conferring enhanced growth and survival propensity.[221] About 40% of ER-positive breast cancers harbor activating PIK3CA mutations.[218] Tumors carrying PIK3CA mutations may respond to PI3K/AKT/mTOR inhibitors.[222]

In endometriosis, PIK3CA mutation is reported in the context of its link with ovarian cancer [223,224] but none was found among 23 patients with only endometriosis,[87] possibly due to the lack of adequate statistical power. However, PI3K/AKT/mTOR signaling pathway has been strongly implicated in the development of endometriosis.[190,225-229] PDK1 overexpression also has been reported in endometriosis.[230]

Activating PIK3CA mutation has been implicated in several fibrotic diseases. It is reported to be found in 83% of radial scars with epithelial atypia[231] and in 90% of patients with fibroadipose hyperplasia,[232] a nonmalignant progressive segmental overgrowth of fibrous and adipose tissues.

In hepatocellular carcinoma, the accelerated tumorigenesis is reported to be attributable to increased injury and inflammation, unrestricted oxidative stress, fibrosis, and compensatory increase in hepatocyte proliferation secondary to PDGFRα/PIK3CA/AKT activation and c-Myc overexpression.[233] In lung epithelial cells, IL-17A inhibits autophagy through activation of PIK3CA to interrupt the GSK-3β-mediated degradation of BCL2, which is be primarily responsible for the development and progression of IL-17A-induced pulmonary fibrosis.[234]

Given the above discussion, it seems that PIK3CA expression is likely to be upregulated in endometriosis, which is consistent with the activation of the PI3K signaling pathway. In addition, activating PIK3CA mutation in endometriosis is credible, and there is also a likelihood that PIK3CA upregulation might be attributable to hypomethylation.

5.1.5 | KRAS

RAS proteins, which include H-, K- and N-RAS, the three closely related members with a molecular mass of ~21 kDa, are small GTPases with two conformational states, a guanosine diphosphate (GDP)-bound "off" state and a guanosine triphosphate (GTP)-bound "on" state.[235] Exchange of GDP for GTP results in a conformational change, turning the molecular switch from the "off" to the "on" position. Ras proteins activate a wide array of downstream signaling pathways with a multitude of effector proteins, including Raf/ERK and PI3K/AKT.[236] ERK1/2 have several substrates, including EGF and estrogen receptors (ERs).[236] They function as intracellular switches in signal transduction cascades that regulate many biological functions including proliferation, apoptosis, and differentiation,[237] which all play important roles in fibrogenesis.

Oncogenic KRAS is encoded by KRAS-2 gene,[235] is downstream of EGFR and an essential component of the EGFR signaling cascade.[238] It is frequently mutated in many malignancies, such as colorectal cancer (~40%), lung cancer (~25%), and pancreatic cancer (~90%).[239,240] The activating mutation of KRAS isolates the EGFR pathway from the effect of EGFR2, rendering EGFR inhibitors ineffective.[241] KRAS also can be activated by TGF-β1,[242] angiotensin II,[243] EGF,[244] endothelin-1,[245] PDGF,[246] and thrombin.[247] Importantly, these genes/molecules or their receptors (eg, angiotensin II receptors AT-1 and AT-2) are all reported to be overexpressed/elevated in endometriosis.[74,248-251]

KRAS mutation attracted much attention after the report that the activation of a Kras allele resulted in peritoneal endometriosis in mice.[150] Since in this model the onset of endometriosis appeared to be quite late (~8 months after conditional induction of K-ras),[150] there is question as whether this mouse model of endometriosis truly recapitulates the human counterpart. Indeed, KRAS activating mutation is reported to be rare in presumably OMA,[87] even though elevated KRAS expression in eutopic endometrium in women with endometriosis has been reported.[252-254] The somewhat prolonged latency period in inducing endometriosis seems to suggest that the KRAS mutation alone may not be sufficient to induce endometriosis. Indeed, well over a decade has been passed since the report on the K-ras induced endometriosis in mouse, but the model does not seem to gain any traction in the mainstream research, even though the transplantation of steroid-manipulated, menstrual like endometrium from conditionally activated K-ras (K-ras$^{G12V/+}$/Ah-Cre$^{+/+}$/ROSA26R-LacZ$^{+/+}$) mice into gonad-intact immune-competent wild-type mice also induced endometriosis.[255]This mouse model of endometriosis also shows that the growth of lesions is ER-dependent since estrogen antagonism suppresses the lesion growth.[255] In addition, the lesions exhibit fibrosis as seen by marked collagen deposition.[255]

KRAS mutations have been identified in 12 (29%) of 42 endometriosis-associated ovarian low-grade endometrioid adenocarcinomas.[256] Inactivating mutation has recently reported in DE lesions.[51]

ERK activation has been reported to be a necessary step in the induction of EMT[257] which plays a critical role in fibrogenesis. While TGF-β1 is well-documented to induce EMT,[258] the intracellular signaling responsible for this induction includes activation of ERK1/2,[259,260] p38 MAPK,[257] and JNK.[261] Again, ERK1/2, p38 MAPK, and JNK have all been reported to be involved in endometriosis.[262-267]

Activated KRAS can cooperate with Snail to promote fibrosis.[268] One important mechanism underlying this promotion is through the induction of Stem-Cell Factor (SCF) and the enhancement of mast cell infiltration.[268] SCF neutralization can block Snail-induced migration of mast cells.[268] In addition, MT1-MMP can cooperate with KRAS to promote pancreatic fibrosis through enhanced TGF-β1 signaling.[269] Importantly, SCF levels are found to be elevated in the peritoneal fluid from women with endometriosis[270] and the expression levels of c-Kit, the receptor for SCF, are reported to be elevated in ectopic endometrium.[271] And increased mast cell infiltration in lesions also has been well-documented,[272,273] especially in DE.[274] MT1-MMP expression has been consistently to be documented to be elevated in ectopic endometrium[275] and also reported to be elevated in peritoneal fluid[276] and eutopic endometrium[277] from women with endometriosis.

Thus, there is reason to believe that KRAS mutation in endometriosis is possible but may be rare. It is very likely to be activated in endometriosis.

5.1.6 | PPP2R1A

The phosphorylation/dephosphorylation of proteins is controlled by protein kinases and protein phosphatases (PP), which plays a critical role in regulating a variety of cellular processes. PPP2R1A encodes the enzyme serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform, and is implicated in the negative control of cell growth and division.[278] Its mutation is reported to be common in the serous type of endometrial cancer.[279] All subunits of PP2A can and have been be mutated in cancer, but PPP2R1A, has the highest mutation rate.[280] Activating PPP2R1A mutations have been reported in 7.1% of patients with ovarian clear cell carcinoma in 2010.[203] Since then, there has been a moderate interest in PPP2R1A mutations in endometriosis-associated ovarian cancer but its mutation is found to be rare.[281,282]

There are scanty reports on the role of PPP2R1A in fibrogenesis. However, one study reports that forced miR-16 expression suppressed the activation of HSCs, which is the critical event in liver fibrogenesis, likely through negative cell-cycle regulation, enhanced fibrolysis, and increased apoptosis.[283] Subsequent integrative analysis identified the regulatory network of miR-16 and found that PPP2R1A is a target of miR-16 and that PP2R1A constitutes a key regulatory network node that mediates the miR-16 action in proliferation, ECM deposition, and survival.[283] Interestingly, treatment of endometriotic cells with peritoneal fluid from women with endometriosis reduced the expression of miR-16.[284,285] Thus, there is a possibility that miR-16 downregulation may induce PPP2R1A activation, facilitating the progression of fibrogenesis in endometriosis.

Note that PPP2R1A is part of the protein phosphatase 2 (PP2 or PP2A), an enzyme coded by the PPP2CA gene.[286] PP2A is a major cellular phosphatase that regulates many protein targets. Its substrate includes cellular proteins, viral proteins, and protein kinases. It functions as a heterotrimeric complex consisting of a catalytic subunit C and two regulatory subunits, A and B.[287] Its specificity, (sub)cellular localization, and catalytic activity are determined by the unique combination of regulatory subunits associated with the catalytic subunit.[287] Moreover, the catalytic subunit is subject to two types of posttranslational modification, phosphorylation and methylation, which can also be important regulatory devices. The A regulatory subunit is encoded by one of two genes α (PPP2R1A) and β (PPP2R1B), which are 86% identical.

The phosphatase activity of PP2A is present in the subunit C and it can dephosphorylate various transcription factors and protein kinases, including MEK, ERK1/2, AKT, and sphingosine kinase (SK).[288] PPP2R1B is reported to be downregulated in cultured dermal fibroblasts from patients with systemic sclerosis, a fibrotic disorder.[289] The reported PPP2R1A activating mutation (p.S256F)[51] is shown recently in endometrial cancer cells to behave in a dominant-negative manner due to gain-of-function interactions with the PP2A inhibitor TIPRL1, resulting in hyperphosphorylation of AKT, GSK3β, and mTOR signaling pathways.[290] That is, the activating mutation leads to reduced PP2A activity and consequent increased AKT activity. PP2A negatively regulates Wnt/β-catenin and ERK.[291]

Reduced PP2A activity has been shown in many cancers and Alzheimer's disease.[292-295]. Hence, PP2A is considered as a tumor suppressor.[296]

Yet PP2A inactivation is involved in fibrogenesis. Both trichostatin A (TSA), a pan-HDAC inhibitor, and HDAC4 knockdown are reported to be sufficient to decrease phosphorylation of AKT and block TGF-β1-stimulated α-SMA expression and thus fibroblast activation, and the pharmacological inhibition of PP1 and PP2A rescues the α-SMA expression in response to TGF-β1.[297] In other words, suppression of PP2A and PP1 is sufficient to facilitate TGF-β1-induced FMT.

In contrast to normal fibroblasts that undergo apoptosis upon collagen matrix, the lung fibroblasts from patients with idiopathic pulmonary fibrosis (IPF) are reported to have low expression of $\alpha_2\beta_1$ integrin, the major receptor for collagen, resulting in a failure to activate PP2A, which, in turn, leads to aberrant activation of β-catenin pathway and subsequent increased proliferation of fibroblasts.[298] Similarly, myofibroblasts on fibrillar type I collagen had reduced PTEN and $\alpha_2\beta_1$ integrin expression as well as reduced PP2A activity, leading to increased AKT, but not ERK, activity, and enhanced proliferation.[299] Overexpression of the catalytic subunit of PP2A or just PP2A is found to impair cardiac function and to promote fibrosis.[300,301]

Taken together, the above discussion strongly suggests that PPP2R1A mutation is likely to reduce PP2A activity, resulting in enhanced fibrogenesis. Increased PPP2R1A expression or reduced PP2A activity has not been reported, but this might be due to the fact that downregulated genes are less likely to be reported unless the genes play critical roles in pathogenesis or pathophysiology. It is likely that PPP2R1A expression is increased in endometriosis. Alternatively, PP2A activity might be reduced.

5.2 | Mutations in ALK, BRAF, FGFR3, GNAQ, NF1, NF2, NOTCH1, and NRAS in endometriosis and their roles in fibrogenesis

5.2.1 | ALK

ALK encodes for anaplastic lymphoma kinase, also known as ALK tyrosine kinase receptor or CD246, which is an enzyme that plays an important role in brain development.[302] Its fusion with various genomic partners is reported to result in constitutively activation and drive tumorigenesis.[302,303] Its expression or mutation has never been reported in endometriosis. There is no documentation of its direct role in fibrogenesis.

5.2.2 | BRAF

BRAF is a well-known protooncogene that encodes for B-Raf, which belongs to the RAF kinase family, and plays a role in regulating the MAPK/ERKs signaling pathway that regulating cell division, differentiation, and secretion.[304] Its activating mutations have been reported in many cancers.[305] BRAF mutation is not found in endometriosis[87] and is found to be rare even in ovarian cancer or endometrial cancer-related endometriosis.[256,306] Despite these negative findings, one study found that BRAF is overexpressed in endometriosis.[307] Another study reports that treatment with PLX4032, a potent-specific BRAF inhibitor, decreased ERK1/2 activity in endometriotic epithelial and stromal cells, with subsequent decreased proliferation, suggesting that the BRAF pathway may be functional in endometriotic lesions.[308]

BRAF is found to be overexpressed in tissue samples from IPF,[309] but a recent study on lung cancer associated with IPF reports that BRAF mutation is found only in a patient with drug-induced pulmonary fibrosis.[310] There is no documentation of its role in fibrogenesis.

5.2.3 | CDKN2A

Cyclin-dependent kinase inhibitor 2A (CDKN2A) is a TSG which encodes for two proteins, $p16^{INK4a}$, a CDK inhibitor, and $p14^{arf}$, a p53 stablizer, from two independent promoters. Inactivation of CDKN2A due to either mutation or hypermethylation can result in alteration in the CDK pathway and tumorigenesis. Somatic mutations of CDKN2A are common in many cancers.

LOH at $p16^{INK4a}$ in endometriosis is reported at the turn of this century.[85] Aberrant methylation at $p16^{INK4a}$ also was reported in 2002 [151] but a more recent study failed to find such an aberration.[87] Expression of $p16^{INK4a}$ was reported to be reduced in endometriosis.[311] Treatment of endometriotic stromal cells with HDAC inhibitors is reported to induce an accumulation of acetylated histones and in the promoter regions of $p16^{INK4a}$, suggesting that the $p16^{INK4a}$ expression is likely to be low in endometriosis.[312] Indeed, suppression of C/EBPα downregulates $p16^{INK4a}$ and CDK4.[217]

Because of its role in regulating cell cycles, $p16^{INK4a}$ is often used, along with $p21^{CIP1/WAF1}$ and senescence-associated ß-galactosidase (SA-β-gal), as a marker for cellular senescence. Since senescence limits fibrogenesis,[110] activation of $p16^{INK4a}$ may signal cellular senescence and thus restrict fibrotic progression. Consistent with this view, it is reported that the expressions of senescence-associated genes p21, p16 , and p27 are upregulated in keloids fibroblasts exposed to X-ray radiation, which may explain as why X-ray radiation is part of the effective therapy for keloids since the radiation may prevent the recurrence of keloids by suppressing fibroblast proliferation, and arresting the cell cycle through inducing premature cellular senescence.[313] Similarly, expression of $p21^{CIP1/WAF1}$, SA-β-gal, and $p16^{INK4a}$ is found to be increased in perivascular fibrotic areas after transverse aortic constriction, and these senescent cells are found to be predominantly myofibroblasts, indicating that some myofibroblasts are undergoing premature senescence in the heart.[314] Inactivation of the premature senescence program by genetic ablation of both p53 and $p16^{INK4}$ leads to aggravated fibrosis in mice after transverse aortic constriction.[314] More interestingly, cardiac-specific expression of CCN1 (CYR61), a potent inducer of premature senescence,[315] resulted in substantial reduction of perivascular fibrosis after transverse aortic constriction.[314] While CCN1 has been consistently reported to be upregulated in endometriotic lesions,[196,316,317] it should be noted that "older" lesions, which have higher fibrotic content than "younger" ones,[62] appear to have diminished CCN1 expression,[316] suggesting that reduced cellular senescence in older lesions permits fibrogenesis.[110] Of course, CCN1 may be important in the establishment of lesions.[316,318]

Given the above discussion, there are reasons to believe that CDKN2A may be downregulated, hypermethylated or even inactively mutated in *older* lesions that have a high fibrotic content, resulting in attenuated cellular senescence in myofibroblasts in lesions.

5.2.4 | FGFR3

FGFR3 encodes for fibroblast growth factor receptor (FGFR) 3 and is a member of the FGFR family. It is considered as an oncogene and is frequently mutated in cancers.[319] FGFR3 overexpression is reported in IPF.[320] But one recent study on lung cancer associated with IPF reports that no FGFR3 mutation is found in patients with IPF.[310] FGFR3 has no documented role in fibrogenesis.

FGFR3 mutation has not been reported in endometriosis,[87] but its ligands FGF1 and FGF2 have been reported to be overexpressed in endometriosis.[321] Given the lack of any direct role in fibrogenesis, it is likely that FGFR3 is not mutated in endometriosis.

5.2.5 | GNAQ

GNAQ gene encodes for guanine nucleotide-binding protein G(q) subunit α, and its activating somatic mutations result in increased MAPK signaling pathway and is found in Sturge-Weber syndrome that increases the malignancy potential.[322] GNAQ mutation or expression has never been reported in endometriosis as of writing, nor has it been documented to play a direct role in fibrogenesis.

5.2.6 | NF1

NF1 encodes for neurofibromin 1 and its mutations are associated with neurofibromatosis type I and Watson syndrome.[323] It is considered as a TSG, and its inactivating mutations or loss leads to RAS hyperactivation, resulting in increased activity of its downstream effectors, such as PI3K/AKT/mTOR and MAPK.[240] Interestingly, NF1 mutation is found only in endometriosis-associated ovarian cancer,[282] but its expression is found to be *reduced* in OMA.[96]

Decreased expression of NF1 is reported to contribute to EMT in neurofibroma specimens and NF1-derived Schwann cells.[324] In a murine fracture model, increased fibrosis is found in Nf1 (null) mouse.[325] Another study reports that forced miR-16 expression suppressed the activation of HSCs (fibroblasts), and NF1 is identified to be one of the key nodes in the functional layer of a regulatory network that mediates the miR-16 action in proliferation, ECM deposition, and survival.[283] Aside from these reports, the role of NF1 in fibrogenesis appears to be limited.

5.2.7 | NF2

NF2 also is a tumor suppressor and encodes for neurofibromin 2, also known as Merlin, which suppresses mTORC1 and the complex formation of SRC/FAK, hence regulating PI3K and RAS/MAPK signaling pathways.[326,327] Nearly 75% of malignant mesothelioma has inactivating NF2 mutations.[328] Merlin also is known to negatively regulate Yes-associated protein (YAP), an effector of the Hippo signaling pathway.[329] Merlin can also inhibit Wnt/β-catenin signaling through inhibiting phosphorylation of β-catenin, thus blocking the translocation of β-catenin from membrane to nucleus by inhibiting dissociation of β-catenin from adherens junction.[330,331]

While NF2 expression or mutation has never been reported in endometriosis, YAP overexpression has.[332] The involvement of Wnt/β-catenin signaling pathway in endometriosis,[70,333] especially in the context of fibrogenesis,[128] also has been reported. Incidentally or not, YAP acts as critical regulators of HSC activation upon chronic injury, and pharmacological inhibition of YAP prevents HSC activation in vitro and fibrogenesis in vivo.[334] In IPF, both YAP and TAZ expression levels are elevated and display a predominantly nuclear localization, which indicates increased transcriptional activity.[335] The elevated YAP and TAZ expression also corresponds to the increased levels of nuclear β-catenin and phosphorylated R-Smads found in fibrotic tissues,[335] suggesting that three signaling pathways, ie, TGF-β/Smad, Wnt/β-catenin, and the Hippo, converge to regulate fibrogenic processes.[336]

In light of these discussions, it seems likely that NF2 expression is likely to be reduced in endometriotic lesions. One might also see NF2 inactivating mutations in lesions.

5.2.8 | NOTCH1

NOTCH1 encodes a member of the Notch family of receptors. Notch is an evolutionarily conserved intercellular signaling pathway that regulates interactions between physically adjacent cells and plays many roles in regulation of cell-fate acquisition,[337] such as survival or apoptosis, proliferation, differentiation, and maintenance of stem-cell quiescence and identity.[338] In mammalians, there are four Notch receptors (NOTCH1-4) and five ligands (Jagged1, Jagged2, Delta-like ligand (Dll)1, Dll3, and Dll4).[339]The NOTCH1 protein has such diverse functions that the gene is considered both an oncogene and a tumor suppressor.[340] NOTCH1 inactivating mutations have been found in cutaneous and lung squamous cell carcinoma,[341] and also in sun-exposed physiologically normal skin[342]

NOTCH1 overexpression has been shown to facilitate the myofibroblast differentiation from lung fibroblasts[343] and to induce COL1A1 and COL1A2 expression in airway fibroblasts,[344] suggesting a possible role of Notch1 in fibrogenesis. Activation of Notch1 signaling has also been reported to induce EMT, while Notch1 suppression reverses the EMT process both in vitro and in vivo.[345,346] NOTCH1, along with its ligand Jag1, has been shown to be regulated by TGF-β1, induce EMT, proliferation, and renal fibrosis in mouse and humans.[347] Jagged1-NOTCH1 signaling also has been shown to be activated in keloid tissues, a fibrotic disease,[348] and in hypertrophic scar formation. Activation of NOTCH1 with Dll4 causes a premature cellular senescence and maladaptive repair, facilitating renal fibrogenesis.[349] NOTCH1 and TGF-β1 are shown to be responsible for the induction of Hes1, an important gene for HSC activation.[350] In contrast, conditional ablation of NOTCH1 attenuates pulmonary fibrosis through reduced myofibroblast activation and expression of α-SMA and collagen I,[351] and inhibition of Notch signaling attenuates Schistosomiasis-induced hepatic fibrosis via suppression of macrophage M2 polarization.[347]

In endometriosis, Musashi-1, a positive regulator of NOTCH1 through suppression of NOTCH1 inhibitor NUMB, has been shown to be elevated.[353] NOTCH1 expression has been reported to be increased in peritoneum adjacent to endometriotic lesions,[354] although it is found to be decreased in eutopic endometrium in women with endometriosis, along with Jagged2 and Dll4.[355] The expression of c-Myc, one NOTCH1 downstream gene, has been well-documented to be increased in endometriosis.[97,356–358] Suppression of NOTCH1 results in reduced lesion size in a murine model of endometriosis.[359] NOTCH1 mutation has been reported in endometriosis-associated ovarian cancer.[282] Recently, the profibrotic role of ADAM17/NOTCH signaling induced by oxidative stress in endometriosis has been reported.[360]

To summarize, it seems that NOTCH1 signaling pathway is likely to be activated in endometriosis. It is likely that NOTCH1 expression may be increased

5.2.9 | NRAS

NRAS is a member of the RAS family, and is mutated in 18%-28% of melanoma.[239,240] Direct sequencing did not find NRAS mutation in 23 lesion samples,[87] but NRAS upregulation is reported in

TABLE 2 Summary of compiled findings regarding mutation and expression of the cancer driver genes in endometriosis and fibrogenesis

Gene	Chromosomal location	Role in tumorigenesis	Mutations reported in benign conditions	Mutation in endometriosis	Expression in endometriosis	Possible roles in fibrogenesis
TP53	17p13.1	Tumor suppressor	Inactivating mutation in rheumatoid arthritis[138,139]	Found in adjacent to ovarian cancer,[83] also loss.[84]Negative reports also.	Mixed results.Likely to be downregulated	TP53 loss suppress senescence of activated fibroblasts, promoting fibrogenesis
PTEN	10q23.3	Tumor suppressor		Inactivating,[51]One reports 21% in OMA[147]; Another reports 53% [148]	Reduced expression in endometriosis.[151-153]	Activates the PI3K/AKT signaling pathway, suppresses the apoptosis of fibroblasts, and enhances their proliferation and invasiveness. Initiates SMAD3- and TP53-dependent fibrotic response
ARID1A	1p36.11	Tumor suppressor		Inactivating,[51]Partial or complete loss of expression,[46,48,206]		Loss of ARID1A promotes wound regeneration
PIK3CA	3q26.32	Oncogene	Soborrheickeatosis: ~16%Fibroadipose hyperplasia: 90%	Activating, Also reported in the context of its link with ovarian cancer[223,224]	Activated PI3K/AKT/mTOR signaling pathway has been implicated[190,225-229]	Not documented.
KRAS	12p12.1	Oncogene		Activating[51]	Upregulated in eutopic endometrium[252-254]	Induction of ERK1/2 and in cooperation with Snail.
PPP2AR1	19q13.41	Oncogene		Activating [51]	NR	Impair PP2A activity
ALK	2p23.1	Oncogene	Inflammatory myofibroblastic tumor: ~50%[53]	NR	NR	Not well documented
BRAF	7q34	Protooncogene	Melanocytic nevi: 70-88% [53]	NR	Overexpressed[307]	Not well documented
CDKN2A	9p21.3	Tumor suppressor		LOH.[85] Aberrant methylation[151]	Reduced expression of p16[311]; Likely to be low[312]	A marker for cellular senescence, which can restrict fibrogenesis
FGFR3	4p16.3	Oncogene		NR	NR	Not documented
GNAQ	9q21.2	Oncogene	Sturge-Weber syndrome: 88%[53]	NR	NR	Not documented
NF1	17q11.2	Tumor suppressor	Neurofibromas and pilocyticastrocytomas[53]	only in endometriosis-associated ovarian cancer[282]	*Reduced* expression in OMA[96]	Not well documented
NF2	22q12.2	Tumor suppressor	Schwannomas, meningioma, glioma and ependymomaastrocytomas[53]	NR	NR	Its suppression is likely to promote fibrogenesis through interaction with Hippo, TGFβ and Wnt-β-catenin pathways
NOTCH1	9q34.4	Tumor-suppressive and Oncogenic	Sun-exposed skin[53]	NR	Increased expression in peritoneum adjacent to endometriotic lesions[354]	Facilitates FMT and fibrogenesis
NRAS	1p13.2	Oncogene	Melanocytic nevi: 6%-14%[53]	NR	Overexpressed[307]	Not documented

ALK, anaplastic lymphoma kinase; ARID1A, the AT-rich interactive domain 1A; FGFR3, Fibroblast growth factor receptor 3; PTEN, phosphatase and tensin homolog deleted on chromosome 10; NF1, Neurofibromin 1; NF2, Neurofibromin 2; OMA, ovarian endometrioma; NR, not reported.

endometriosis.[307] However, there is no documentation of its role in fibrogenesis.

5.3 | Variations on a major theme

Admittedly, there are more TSGs and oncogenes (eg, GSTP1, SOCS1, RASSF1, APC, and YAP, just to name a few) that are not included for this review, but the choice of the 6 + 9 = 15 driver genes is based on the considerations that (a) whether it has ever been reported to be mutated in endometriosis; and (b) it may be pointless, and perhaps impossible, to review all cancer drive genes—one has to step somewhere, somehow. In this sense, the list in Kato et al[53] provides a good compromise for the choice of a "control" set that is not prohibitively too large or inherently biased. Thus, there is no a priori selection bias to choose the NR set. Nonetheless, one overwhelming message gleaned from this overview is that all six cancer driver genes in the RP set are all involved in fibrogenesis. This is in stark contrast to only three (CDKN2A, NF2, and NOTCH1) out of nine driver genes in the NR set that have been credibly documented in fibrogenesis (Table 2), the difference is statistically significant ($P = 0.028$, by Fisher's exact test). Even if NF1 is counted to have some profibrotic capability, the difference is still statistically significant ($P = 0.044$, by Fisher's exact test).

Figure 2 summarizes the above discussion by anchoring the nine cancer driver genes (in solid background) in a vast sea of discoveries reported in endometriosis. Among the nine genes, six are from the RP set and the remaining three, the NR set. It can be seen from the figure that the diagram pieces together many genes/proteins reported to be aberrantly expressed in endometriosis that are otherwise scattered in the ever-growing literature. It highlights fibrosis as the final destiny of all endometriotic lesions if unimpeded, and provides a more coherent account for many culprits, aiders and abettors involved in EMT and fibrogenesis in endometriosis. In addition, it seems that several pathways lead to the activation of the PI3K/AKT signaling pathway, underscoring its vital importance in fibrogenesis of endometriosis. In fact, this is consistent with the

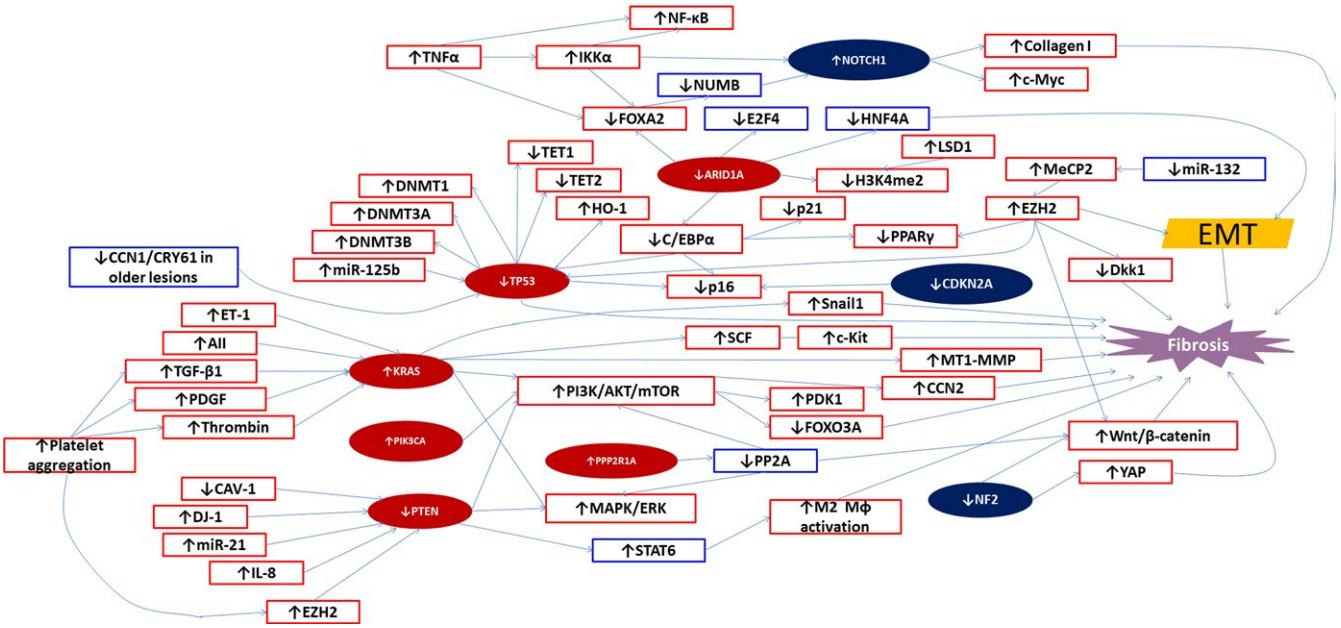

FIGURE 2 Waiving a tapestry of possible gene network involved in fibrogenesis that anchors the cancer driver genes reported or unreported to be mutated in endometriosis. The genes/proteins in solid maroon oval are those genes reported to be mutated in endometriosis, while those in solid dark blue oval are those that have not been reported to be mutated. The genes/proteins within the red rectangles are those that have been reported in the literature, while those within the blue rectangles are those that have not been reported. ↑ means activating mutation or overexpressed gene/protein, while ↓ indicates an inactivating mutation or overexpressed gene/protein. → means "leads to", "results in", or "induces". AII, Angiotensin II; ARID1A, the AT-rich interactive domain 1A; CAV-1, caveolin-1; C/EBPα, CCAAT-enhancer-binding protein α; CCN1/CRY61, CCN family member 1/cysteine-rich angiogenic inducer 61; DNMT, DNA methyltransferase; E2F4, E2F transcription factor 4; ERK, extracellular signal-regulated kinase; ET-1, endothelin 1; EMT, epithelial-mesenchymal transition; Dkk1, dickkopf homolog 1; FOXO3A, forkhead box O3A or FOXO3; H3K4me2, dimethylated histone 3 lysine 4; HNF4A, hepatocyte nuclear factor 4α; LSD1, lysine-specific demethylase 1; PDGF, platelet-derived growth factor; EZH2, enhancer of zeste homolog 2; FOXA2, forkhead box A2; HO-1, hemeoxygenase 1; IKKα, inhibitor of nuclear factor kappa-B kinase subunit α; mTOR, mammalian target of rapamycin; MeCP2, methyl CpG-binding protein 2; MAPK, mitogen-activated protein kinase; Mφ, macrophage; MT1-MMP, membrane-type 1 matrix metalloproteinase, also called matrix metalloproteinase-14 or MMP-14; NF1, Neurofibromin 1; NF2, Neurofibromin 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDK1, Pyruvate dehydrogenase lipoamide kinase isozyme 1; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PP2A, protein phosphatase 2; PPARγ, peroxisome proliferator-activated receptorγ; PTEN, phosphatase and tensin homolog deleted on chromosome 10; SCF, stem cell factor; STAT6, Signal transducer and activator of transcription 6; TET, ten-eleven translocation methylcytosine dioxygenase; TGF-β1, transforming growth factor β1; TNFα, tumor necrosis factor α; YAP, Yes-associated protein

published studies demonstrating its involvement in endometriosis development.[155,229,361,362]

Moreover, it also lists several suspects, such as miR-132, HNF4A, STAT6, and E2F4, that so far have not ever been reported to be involved in endometriosis but are very likely to play important roles in the development of endometriosis.

In fact, it has been reported that IKKα, induced by TNFα, can suppress NUMB and thus activate NOTCH1 through suppression of FOXA2.[363] HNF4A activation has been reported to attenuate liver fibrosis through suppression of EMT.[364] Combined activation of HNF4A, HNF1A, FOXA3, and GATA4 has been reported to reprogram hepatic myofibroblasts into hepatocytes in vivo, suppressing liver fibrosis,[365] raising the possibility of reversing fibrosis through transcriptional reprogramming via activation of select transcription factors. Importantly, increased IKKα expression has been reported in endometriosis[366] and so have TN pronounced in mice that had lesions mor pronounced in mice that had lesions mor Fα[367] and Musashi-1, a negative regulator of NUMB, which suppresses NOTCH1.[353] Incidentally, ovarian-like differentiation in endometriotic lesions is found to be associated with increased expression of GATA4/6.[368]

It should be noted that this diagram is by no means all-inclusive and complete. As we understand more about the pathogenesis and pathophysiology of both endometriosis and fibrogenesis, there is no doubt that we should have a better grasp of the complexity of endometriosis.

5.4 | Do driver mutations occur before or after lesions are formed?

Aside from reporting mutations in four cancer driver genes, Anglesio et al also reported a patient with DE who harbored an identical c.35G→A (p.G12D) KRAS mutation in three distinct DE lesions and also in normal sampling of eutopic endometrial and endocervical epithelium.[51] Since the mutation occurred in normal endometrium and the endocervix, the finding raises the issue as whether or not the mutation is an early event occurred before any lesion is formed.

This issue is probably better framed in a bigger context. One most widely accepted theory for the pathogenesis of endometriosis is Sampson's retrograde menstruation theory. However, retrograde menstruation has been reported to be nearly universal for women with patent fallopian tubes.[369] Given the moderate prevalence of endometriosis,[1] several theories have been proposed to explain the vast gap between the moderate prevalence and the ubiquity of retrograde menstruation. One view, expressed by many papers, is that endometriosis may be an endometrial disease, in the sense that the eutopic endometrium may have already harbored molecular/cellular aberrations that predispose their host to endometriosis (see, for example[370]). However, a close inspection of all articles documenting the aberrations indicates that these data are all based on patients who have *already* been diagnosed with endometriosis. Hence, it is unclear whether these aberrations are the cause or merely the consequence of endometriosis. Unfortunately, experimental data that support this hypothesis are lacking.

In contrast, there are experimental data that actually provide the evidence that all these endometrial aberrations may well be the *consequence* of endometriosis. Lee et al reports that, 14 weeks after mice received surgically placed endometrial fragments from donors, their eutopic endometrium showed aberrant gene expression as well as aberrant DNA methylation.[371] Similar data have also been reported by baboon models of endometriosis.[372] A recent study even showed that 12 weeks after surgical induction of endometriosis, the eutopic endometrium showed altered gene expression which became more pronounced in mice that had lesions more proximal to their uteri than their counterpart that had distal lesions.[373]

A close examination of the finding by Anglesio et al actually shows that the mutation is unlikely an early event. As figure 4 in Anglesio et al shows, the patient harbored identical KRAS mutation in three distinct DE lesions and also in normal sampling of eutopic endometrial and endocervical epithelium.[51] Importantly, the allelic frequency of the mutation in the three DE lesions and normal sampling of eutopic endometrial and endocervical epithelium were 38.57%, 31.22%, 9.37%, 0.28%, and 0.05%, respectively. In other words, the allelic frequency is one to two orders of magnitude higher in DE lesions than that in eutopic endometrium and endocervix.

Since all current cells in an organism descended from a single cell (fertilized egg) through successive cell divisions, there is reason to believe that the mutation that the three lesions, the eutopic endometrium, and the endocervix shared came from the same common ancestor cell, as shown in Figure 3. It is well known in phylogenic analysis that clones with higher mutation frequency harbored the mutation longer than those with lower frequencies, simply because the former had more chances than the latter to propagate.[374] In other words, the mutations harbored by DE lesions existed in longer time than those in eutopic endometrium and the endocervix (Figure 3), and the mutation occurred in normal tissues resulted from clonal expansion and/or diffusion originating from the DE lesions due to increased invasiveness of endometriotic epithelial cells resulting from EMT. As argued in the above, mutations occur because of selection pressure, and now given the evidence that DE lesions harbor mutations longer than that of normal tissues, it can be concluded that driver mutations must occur *after* lesions are formed. Otherwise, a nearly 100% mutation frequency in lesions or higher mutation frequency in normal tissues adjacent to the DE lesions would have been observed.

It is a pity that the study by Anglesio et al did not capitalize the opportunity to further sequence these samples. If they did, they could have been able to use the sequence data to reconstruct a precise phylogenic relationship among these tissues, possibly elucidating the lineage relationship among these tissues.

6 | CHANGING PRESSURE FOR GENOMIC ALTERATION DUE TO OXIDATIVE STRESS

Oxidative stress has been well-documented to be involved in the pathophysiology of endometriosis.[375] DNA is particularly vulnerable

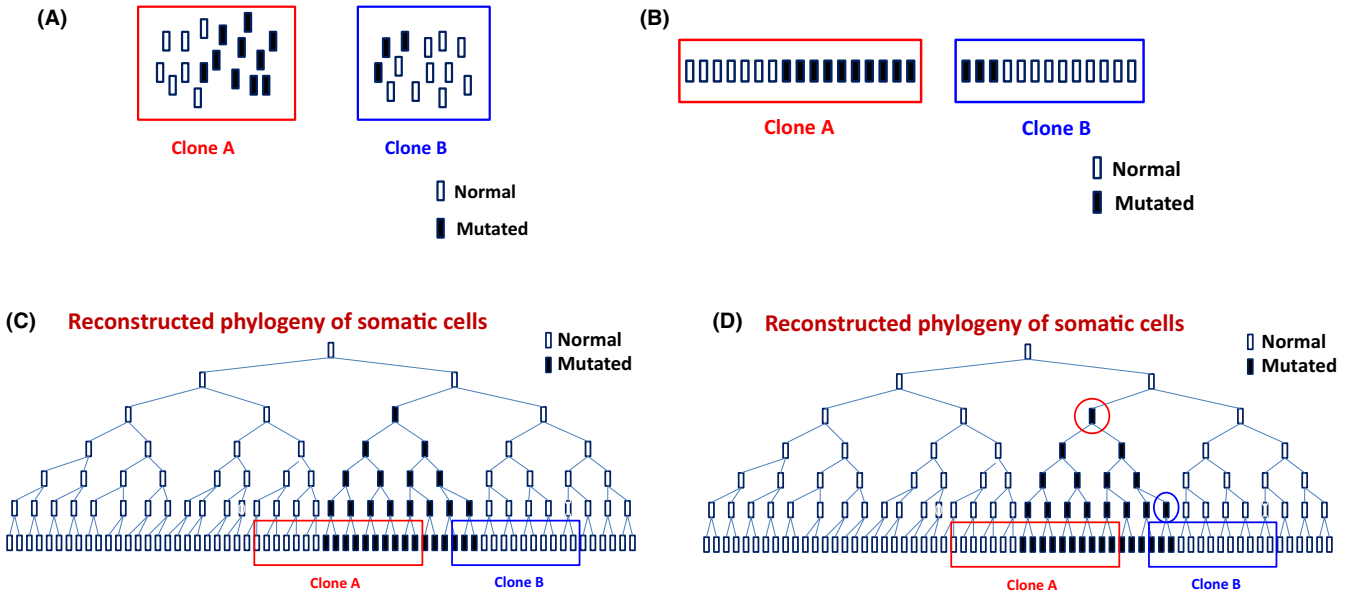

FIGURE 3 A cartoon illustration showing that clones with higher mutation frequencies harbored the mutation longer than clones with lower mutation frequencies. A, Two clones or tissue samples, A and B, with different frequencies of the mutant allele. In this case, clone A has a higher frequency of the mutant allele than that of clone B. B and C, Since all somatic cells are descended from their parental cells (ie, by mitosis, one cell gives rise to two daughter cells), all cells in clones A and B, mutated or not, can be arranged based on their genetic similarity—ie, two cells are genetically closer if they share more similarity in terms of DNA sequences. D, For clone A, all cells carrying the mutant allele are descended from one common ancestor cell (circled in red) while all cells with the mutation are descended from the common ancestor cell that is circled in blue. However, this mutated cell, circled in blue, actually descended from the cell, circled in red, that is the common ancestor for all cells with the mutatnt allele in clone A. Therefore, clone A harbored the mutation earlier than clone B. The exact inference of this phylogenetic relationship would require statistical calculations with some very elaborate models. See, for example[374]

to the damaging effect of reactive oxygen species (ROS), as are other biomolecules. The presence or absence of oxidative stress lies in the imbalance between the production of free radicals and their elimination by antioxidants.[376] As ectopic endometrium experiences cyclic bleeding, cell-free hemoglobin and its highly toxic by-products heme and iron are released from erythrocytes in and around lesions. Lysis of erythrocytes by macrophages results in iron overload, inducing iron-mediated damage, oxidative injury and inflammation and oxidative stress.[375] Consistently, granulosa cells from patients with infertility and endometriosis exhibit more signs of severe oxidative DNA damage when compared with cells from other patients with infertility.[377] Expression levels of 8-hydroxydeoxyguanosine (8-Oh-dG), a sensitive indicator of DNA damage resulting from oxidative stress, are reported to be significantly higher in samples of normal ovarian cortex surrounding endometriotic cysts.[378] Interestingly, however, the staining of γ-H2AX, a marker for DNA damage, is found to be decreased as endometriotic lesions aged.[113]

In endometriotic lesions, repeated bleeding and the DNA-damaging molecules secreted by lesions themselves should result in severe oxidative stress and thus impose a strong pressure for mutation on endometroitic cells. However, as DNA damage, oxidative stress, hypoxia, and oncogene (such as KRAS and YAP) activation induce cellular senescence [107] and senescence would curtail fibrosis, it is likely that in older and thus more fibrotic lesions may experience less hypoxia and less oxidative stress (due to increased fibrotic content and thus reduced cellularity, less hemorrhage and thus iron overload) and less DNA damage (as seen by reduced γ-H2AX expression [113]), the pressure for cellular senescence may be reduced, especially in the stromal compartment. This would be consistent with reduced Caveolin-1 expression in adenomyosis,[189] which can be highly fibrotic,[65] especially as lesions get older.[64] This also would be consistent with seemingly progressive decrease in CCN1 expression in older lesions.[316] This dynamic view could also explain the conflicting reports published so far since most, if not all, published studies habitually treat endometriotic cells as if static or even immutable. Obviously, when epithelial cells are differentiated into mesenchymal cells or even smooth muscle-like cells, their phenotypes and functionality change accordingly.

6.1 | Mismatch repair genes in endometriosis

The preservation of genomic integrity is of vital importance to the perpetuation of life. On the other hand, somatic genomic alterations are bound to occur since DNA is susceptible to chemical modifications by endogenous and exogenous agents, although it is less susceptible to replication errors. Thanks to evolution, all cells are equipped with intricate and sophisticated defense systems, such as DNA repair, damage tolerance, cell-cycle checkpoints, and apoptosis that collectively function to safeguard against DNA damage. Through institution of several mechanisms, including base excision

repair, nucleotide excision repair, mismatch repair (MMR), homologous recombination, and nonhomologous end joining, a robust DNA damage response (DDR) is established in different stages of the cell cycle to repair any DNA damage.[379] Interestingly, DDR is activated through the inhibition of PP2A.[380]

Somatic point mutation can conceivably occur due to the failure in base excision repair, nucleotide excision repair, or MMR. In endometriosis, however, only the aspect of MMR has been investigated so far, mostly in the context of potential for malignant transformation.

Higher DNA repair capability in women with endometriosis has been reported.[381] Higher DNA damage and *lower* DNA repair activity have been reported to be related to endometriosis progression, ie, rASRM stage,[382] although the use of rASRM stage as a measurement for disease progression is debatable.

Significant loss of MMR proteins, including MLH1, MSH2, MSH6, and PMS2, that are known to be associated with microsatellite instability (MSI),[383] in the stromal component of ectopic endometrium has been reported.[384] In endometriotic glandular epithelial cells, cytoplasmic staining for aurora A kinase is found to have higher MMR protein expression, suggesting an increased activity of the MMR system.[384]

MLH1 is a member of the MMR system in humans which rectifies errors in DNA replication during mitosis to ensure genomic fidelity. LOH at MLH1 and MSH2 in adenomyosis also has been reported.[385] Transcriptional inactivation of the MLH1 gene through promoter hypermethylation is often associated with MSI,[383] which is reported to be associated with the malignant transformation of endometriosis.[382-386]

Promoter hypermethylation of MLH1 has been found in ~4% (2/46) of endometriotic lesions.[151] Loss of MMR protein expression is reported in 10.1% of endometriosis-associated ovarian carcinomas.[389]

Taken together, there is evidence to suggest that the DDR system appears to be activated but somehow its activity seems to be lowered in endometriosis, raising the prospect of genomic alteration.

6.2 | Endometriotic epithelial cells are more vulnerable than stromal cells to mutational pressure

In endometrium, the coiling and maturation of the spiral arterioles and growth of the subepithelial capillary plexus take place in the secretory phase.[390] After progesterone withdrawal, the luminal portion of the endometrium is shed and the menstruation occurs. This is followed by endometrial repair, which seems to be analogous to classic wound healing and include inflammation, its resolution, angiogenesis, tissue formation, and tissue remodeling or reepithelialization.[390] As in eutopic endometrium, the ectopic endometrium starts in each menstrual cycle with the shedding of glandular epithelial cells, but much less so in the endometriotic stromal cells. This relatively more rapid cellular turnover in epithelium than the stroma may explain, at least in part, as why the mutations are seen only in the epithelial cells but not in stromal cells of DE lesions as reported in Anglesio et al.[51] This seems to be supported by the recent report that of all 19 mutations detected in 24 DE lesions, all were significantly enriched in epithelial but not in stromal components of every lesion examined.[391] The only exception is TP53, since its inactivation, which prevents cellular senescence, is expected to occur in the stromal component of endometriotic lesions, which promotes fibrogenesis.

The presence of mutations in the epithelium, but not in the stroma, of endometriotic lesions suggests that the two cell components do not share the same lineage. This is simply due to the fact that, should they share the same lineage, it is unlikely that the all the driver mutations seen in the endometriotic epithelial cells just occurred after one or more cell divisions, nor could they reverted back to wild types.

Given the most, if not all, studies reporting genomic alterations in endometriosis used careful tissue microdissection techniques[31,51] to evaluate mutations in epithelial and stromal cells separately, one possibility that some studies that failed to find any mutation is because the mixed use of different cell types may have obscured the true signal.

6.3 | Spontaneous somatic mutations in apparently normal tissues are not rare

As noted Anglesio et al[51] and others, spontaneous somatic mutations or genomic alterations in apparently normal tissues and benign conditions are not rare.[53,352,392,393] While the theory of clonal selection of driver mutations drive the progression from benign lesions to premalignancy and then to malignancy appears to hold true, exceptions do exist.[53] In addition, while ARID1A acts as tumor suppressor and KRAS and PIK3CA often behave as oncogenic, their mutation frequencies vary wildly among different cancers, attesting to the notion that cellular context also is important, and that perhaps multiple gene mutations or deregulations may be required for tumorigenesis.

Animal models have shown that endometriosis-like lesions can be induced in mice by activation of KRAS or deletion of PTEN,[150] and a combination of these abnormalities, such as KRAS activation plus TP53 loss,[90] concurrent inactivation of TP53 and Rb1,[394] PTEN loss plus PIK3CA activation,[395] and KRAS activation plus PTEN loss[150] leads to the development of malignant ovarian tumors that resemble endometrial cancer in humans. Thus, these data seem to suggest that more than one driver mutation is needed for malignant transformation.

7 | SOME PREDICTIONS

Given the above discussion, several predictions can be made. First, as lesions become older or more fibrotic, the activated myofibroblasts may become less senescent. Alternatively, lesions exposed to higher concentration of profibrotic milieu should be less senescent, as manifested by decreased expression of TP53, p16, and SA-β-gal, and also reduced expression of CCN1 and caveolin-1.

Second, given the natural history of endometriotic lesions, it seems that the extent of fibrosis should be proportional to the age

of the lesion, which should, in turn, be proportional to the increased frequency of mutations. Consequently, these driver mutations as well as those passenger mutations should be observed primarily in DE tissues with higher fibrotic content. It is unfortunate that the extent of fibrosis in tissue samples used in Anglesio et al[51] was not evaluated—in fact the word "fibrosis" was not even mentioned once in the paper. However, Figure 3A in Anglesio et al[51] seems to show the increased fibromuscular content characteristically DE,[396] very likely a manifestation of SMM.[62,74] Note that this assertion can be easily proven or refuted thorough careful evaluation of the tissue fibrotic content and the mutation status in both driver and passenger mutation genes.

As a corollary, we should expect to see much less frequent mutations in both driver and passenger mutation genes in OMA lesions than that of DE since the extent of fibrosis in OMA is less than that of DE.[71] One possible exception is perhaps ARID1A, since OMA lesions may also be under strong pressure for tissue repair.

Third, reduced expression or inactivation of TP53 and PTEN, due to either somatic mutation or hypermethylation, should be seen mostly in the stromal component of endometriotic lesions. This is mainly due to the former's role in releasing the break on fibrogenesis when inactivated[110] and the latter's role in activating the PI3K/AKT signaling pathway that drives fibrogenesis.

Fourth, since sensory nerve-derived substance P and CGRP accelerate fibrogenesis in endometriotic lesions, and, in particular, the close correlation between the extent of fibrosis and the immunostaining of NK1R, an SP receptor, we should expect to see that DE lesions harboring either passenger or driver mutations also express NK1R. Figure 4 in Anglesio et al[51] is consistent with the locations and the abundance of sensory nerve plexuses seems to correlate with the frequency of activating KRAS mutations in different DE and adenomyotic lesions.

Fifth, those endometriotic lesions showing diminished E-cadherin but increased vimentin or even α-SMA staining in the glandular epithelium may be at increased risk of harboring driver mutations. We have shown recently that DE lesions seem to have undergone more complete and thorough EMT, FMT, and SMM as compared with OMA lesions.[71] Hence, stromal endometriosis, ie, lesions showing the absence of glandular epithelial cells,[397,398] is frequently seen in DE lesions.[399,400] As most driver mutations are reported to occur only in the lesional epithelial cells in DE,[51] these cells may also exhibit lower or even the absence of E-cadherin expression but elevated expression of mesenchymal markers such as vimentin or even markers of smooth muscle cells such as α-SMA.[71] Due to the increased cellular mobility and invasiveness resulting from EMT, patients with these types of DE lesions may be at elevated risk of dissimilating or spreading of endometriotic cells in other locations, and thus risk of recurrence.

Sixth, since CDKN2A, NF2, and NOTCH1 also appear to play critical roles in fibrogenesis of endometriosis (Figure 2), their mutations in endometriosis are also likely. In addition, for the 6 + 3 driver genes play important roles in fibrogenesis (Figure 2), it is likely that we may see their aberrant methylation even if no mutation is found.

Lastly, aside from the use of more complete genomic and epigenomic analyses, studies with larger sample sizes, the employment of tissue microdissection techniques, and the focus on lesions with higher fibrotic content should have increased chance to detect driver mutations in lesions. Smaller sample sizes will compromise statistical power, the use of mixed endometriotic stromal and epithelial cells would obscure the true signals since in many lesions the stromal component comprises ~70% or higher proportion of the entire lesions, especially when the extent of fibrosis is higher.

8 | CLINICAL SIGNIFICANCE

In light of the above discussion, the clinical significance of driver mutations in endometriosis, in particular in DE,[51] can be further illuminated as follows.

First, the driver mutations in endometriotic lesions may not necessarily be synonymous with malignancy or premalignancy. The labeling may incite unnecessary, and perhaps ungrounded, fear or even panic in the patient. As discussed above, the driver mutations may be both the cause and consequence of fibrogenesis. As such, evidence that the presence of these driver mutations would increase the risk of malignant transformation needs to be gathered and carefully analyzed.

Second, mutations suggest permanent, irreversible genomic changes. This could mean that treatment of patients with these genomic alterations would be more challenging. This is especially true for hormonal therapy, which is unlikely to rectify the genomic aberrations.

For those patients whose lesions harbor driver mutations, because of their increased fibrotic content, the vascularity is concomitantly reduced and the PR-B expression levels are also reduced.[71] For these patients, hormonal drug treatment is expected to be ineffective, due to the difficulty in delivering the drug to the intended target tissues and the reduced PR-B expression.

Lastly, in view of the seemingly central role of the PI3K/AKT/mTOR signaling pathway in fibrogenesis in endometriosis (Figure 2), naturally this pathway can be considered as a potential target for therapeutics. Indeed, inhibition of the AKT/mTOR has been reported to be effective in preventing DE in mouse.[401] In addition, Figure 2 also underscores the potential roles of epigenetic modification in intervention, which has shown some promising results in treating adenomyosis.[402,403] Future research is warranted to further explore these potentially profitable avenues.

9 | CONCLUSIONS

As growing evidence indicates, fibrosis is the ultimate fate of all endometriotic lesions without intervention, simply because they are fundamentally wounds undergoing ReTIAR.[12,62,63] Although fibrogenesis takes time, one needs to keep in mind that there is a

well-documented and significant diagnostic delay in endometriosis, typically a mean or median of 7 or more years from the time a patient first experiences symptoms until she receives a definitive diagnosis.[6,404-406] In baboon models of endometriosis, lesions of 1 year or older after induction demonstrate substantial fibrosis.[62] This may explain as why one recurring theme is fibrosis when reviewing the six driver genes in the RP set, while only a portion of the other nine driver genes in the NR set are ever documented to be involved in fibrogenesis.

This review should help to shed more light on the pathophysiology of endometriosis by weaving a tapestry of fibrogenesis network, piecing together many genes/proteins known to have aberrations that are otherwise strewed in the literature. This tapestry, albeit still incomplete, provides more clues to the pathophysiology of endometriosis and represents potential therapeutic targets. For example, we can now appreciate the roles of TP53 inactivation in suppression of senescence in fibroblasts and in promoting fibrosis in endometriosis, as most, if not all, previous studies have focused exclusively on its role in malignant transformation. In fact, through the lens of the ReTIAR and fibrogenesis, we can now understand as why many clinical trials on endometriosis have failed.[407]We can also appreciate the physiological roles of ARID1A downregulation in facilitating tissue repair, which endometriotic lesions encounter almost all the time. In addition, several genes/proteins, such as E2F4 and PP2A, so far have not been reported to be involved in endometriosis, and should be closely scrutinized in future research. Moreover, this review highlights the point made previously that endometriotic lesions are not a static entity; instead, they evolve gradually but progressively to SMM and fibrosis if unimpeded.[74]

While the finding that DE lesions harbor cancer driver mutations is rather surprising, the recently unveiled natural history of endometriotic lesions, coupled with the reported roles in fibrogenesis of these driver gene mutations, tells us that these mutations are likely not the harbingers of imminent malignant transformation. Rather, they may be the result of combined fibrogenesis, mutational pressure due to oxidative stress, and more cell turnover. Consequently, these mutations should not sound undue alarm unless proven otherwise.

Admittedly, the inference drawn above is based on observations made in other cell types or organs. However, as the God does roll dices (hence more cell turnover increases the chance of genomic alterations) and often acts as a tinkerer who makes with existing machinery and tools at hand, there are strong reasons to believe that similar processes occur in endometriotic lesions.

Cell clones with driver mutations have selective advantages over those without, be it faster or more proliferation, or less requirement for oxygen. In many cancers, this manifests as an enrichment of protein-altering mutations in cancer genes compared to that expected for the background mutational rate. However, since the frequency of driver mutations in sun-exposed but physiologically normal skin cells can be high,[342] it may not be so surprising that endometriotic lesions, which are under constant assault of hypoxia, proinflammatory cytokines, and oxidative stress, harbor somehow low-grade driver mutations. As shown elegantly by that article, even the size of clonal expansion induced by a somatic mutation need not to correlate with its potential to induce malignant transformation.[342]

Despite new lights shed on the pathophysiology of endometriosis through this review, there are still many stones that are left unturned. Except knowing that endometriotic cells are under pressure for mutations to gain certain selective advantages, it is unclear as which factor(s) are mainly responsible for causing the mutation. In addition, KRAS and PIK3CA are oncogenes, and their activating mutations, once occur, should activate these oncogenes. However, oncogene activation in a normal cell does not necessarily lead to cell transformation but, instead, induces cellular senescence.[108, 408] Repeated cell division and strong mitogenic signals are also inducers of senescence.[409] Yet senescence restricts fibrosis.[106] So does this mean that the oncogene activating mutations as reported would lead to the restricted fibrosis? Or endometriotic cells have developed some mechanisms that elude senescence? Moreover, consistent with the view that fibrogenesis entails epigenetic aberrations,[410] growing evidence indicates that in endometriosis fibrogenesis also involves epigenetic changes.[61, 71, 411,412] This raises the question as whether hormonal therapeutics can actually modify the epigenetic aberration, resulting in a gradual reverse of fibrogenesis, especially in highly fibrotic lesions such as DE. A recent study reports that, dienogest, a synthetic progestin, is effective in alleviating symptoms but does not reduce nodular size in DE,[413] suggesting that hormonal therapeutics cannot modify the epigenetic aberration that is already in place. This would mean the necessity of taking these drugs for a long period in order to alleviate the symptoms without changing the existing epigenetic aberrations. This, of course, presents an issue for the management of endometriosis, but it also presents an opportunity to explore new avenues for rectifying epigenetic aberrations to achieve better treatment results. Again, future research is needed to clarify these issues.

In summary, cancer driver mutations arise in endometriotic lesions very likely from strong pressure for progressive fibrogenesis. The network anchored by the nine driver genes should help to gain new insight into the pathophysiology of endometriosis. It highlights the powerful pressure of fibrogenesis that endometriotic lesions are experiencing, especially in DE lesions. Given that somatic driver mutations can and do occur frequently in physiologically normal tissues, it is argued that these mutations in endometriosis are not necessarily synonymous with malignancy or premalignancy. The fibrogenesis networks linking all genes of driver mutations and others should point to new therapeutic targets for endometriosis.

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The author declares no conflict of interest. *Human/Animal rights:* This article does not contain any studies with human and animal subjects performed by any of the authors.

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