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REVIEW

The possible role furin and furin inhibitors in endometrial adenocarcinoma: A narrative review

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Abstract

Background: Endometrial adenocarcinoma (EAC) is a malignant tumor of the endometrium. EAC is the most common female malignancy following the menopause period. About 40% of patients with EAC are linked with obesity and interrelated with hypertension, diabetes mellitus, and high circulating estrogen levels. Proprotein convertase (PC) furin was involved in the progression of EAC.

Recent findings: Furin is a protease enzyme belonging to the subtilisin PC family called PC subtilisin/kexin type 3 that converts precursor proteins to biologically active forms and products. Aberrant activation of furin promotes abnormal cell proliferation and the development of cancer. Furin promotes angiogenesis, malignant cell proliferation, and tissue invasion by malignant cells through its pro-metastatic and oncogenic activities. Furin activity is correlated with the malignant proliferation of EAC. Higher expression of furin may increase the development of EAC through overexpression of pro-renin receptors and disintegrin and metalloprotease 17 (ADAM17). As well, inflammatory signaling in EAC promotes the expression of furin with further propagation of malignant transformation.

Conclusion: Furin is associated with the development and progression of EAC through the induction of proliferation, invasion, and metastasis of malignant cells of EAC. Furin induces ontogenesis in EAC through activation expression of ADAM17, pro-renin receptor, CD109, and TGF-β. As well, EAC-mediated inflammation promotes the expression of furin with further propagation of neoplastic growth and invasion.

KEYWORDS
endometrial adenocarcinoma, furin, inflammatory signaling, invasion, metastasis, proliferation

1 | INTRODUCTION

Endometrial adenocarcinoma (EAC) is a malignant tumor of the endometrium causing abnormal vaginal bleeding, dyspareunia, pelvic pain, and dysuria.[1] EAC is the most common female malignancy following the menopause period and presented with irregular vaginal bleeding and clear vaginal discharge.[1] About 40% of patients with EAC are linked with obesity.[1,2] As well, EAC is interrelated with hypertension, diabetes mellitus, and high circulating estrogen level.[3] EAC is the third greatest common cause of death in women following ovarian and cervical cancers.[1,3] EAC is the most common malignant tumor in developed countries and represents 80% of endometrial cancer.[4] Remarkably, the rate of EAC has been shown to increase between 1980 and 2020 due to the growing rate of obesity and the increasing rate of elderly women.[4]

Regarding the molecular classification of EAC, recent studies illustrated four types including DNA polymerase epsilon (POLE) -mutated, copy number low, copy number high, and hypermutated type.[5,6] According to analogous classification system, five types are recorded including POLEmut, mismatch repair (MMR) deficient, p53 aberrant, and no specific molecular profile.[5,6] The National Comprehensive Cancer Network has integrated molecular analysis into its endometrial carcinoma algorithm as a result of the increasing amount of evidence that supports this classification system.[5]

Diagnosis of EAC is done by endometrial biopsy.[4] Molecular biomarkers like DNA ploidy, hormone receptor, p53 level, stathmin, and level of adhesion molecules have been used in the diagnosis and prognosis of EAC.[4] Due to the heterogeneity of EAC, many molecular biomarkers might be not enough for a more accurate diagnosis of this type of malignancy. These methods are not "used" but they were "examined" as a screening serum marker.[7] Diagnosis should be confirmed by histopathologic examination of the endometrial biopsy, and it is the golden standard, and it can be applied as an office biopsy. Currently, there is no molecular diagnostic marker for any disease to replace histopathology. However many molecular markers are under examination for prognostic or therapeutic purposes mainly in EAC. This molecule may be high in endometrial cancer, however, to describe a diagnostic marker, and to report the presence or absence of a condition (here endometrial cancer) we need an accuracy test that describes the sensitivity, specificity, predictive values, and the likelihood ratios.[8] In order to render clinical judgments and direct the provision of patient treatment, healthcare professionals must possess a comprehensive grasp of the probability of a patient's affliction, achieved through the amalgamation of their understanding of pretest probability and diagnostic evaluations. Diagnostic instruments are regularly employed in healthcare environments for the purpose of ascertaining appropriate courses of action; nevertheless, numerous of these instruments are susceptible to fallacy.[8] The identification of EAC is conducted through the use of an endometrial biopsy.[4] Due to the heterogeneity of EAC, many molecular biomarkers might be not enough for a more accurate diagnosis of this type of malignancy. To promote the progress of clinical outcomes in women with EAC, numerous strategies are suggested to reach the primitive diagnosis of EAC particularly in the early stage.[9] Indeed, some biomarkers like micro-RNA, miR223, miR222, and CA-125 can accurately differentiate high and low-risk women with EAC.[9] It has been shown that proprotein convertase (PC) furin was involved in different tumor progressions including EAC.[10] Different studies revealed that furin was the unique PC type linked with the development of EAC as confirmed by endometrial biopsies in postmenopausal women.[11,12] Thus, furin could be a noninvasive tool in the diagnosis of EAC. The rationale of the present study was regarded as due to the involvement of furin in various types of malignancies.[13] Therefore, furin could be a noninvasive tool in the diagnosis of EAC. Therefore, this review aimed to find the association between furin activity and EAC.

2 | FURIN PATHWAY OVERVIEW

Furin is a protease enzyme also named paired basic amino acid cleaving enzyme encoded by the furin gene, involved in the activation of several proteins.[14] Furin belongs to subtilisin/kexin type 3 converts precursor proteins to biologically active forms and products.[14] The substrates of furin are pro-albumin, pro-parathyroid hormone, pro-beta-secretase, transforming growth factor beta-1 (TGFβ-1), von Willebrand factor, and type 1 matrix metalloproteinase.[15] As well, furin is implicated in the pathogenesis of juvenile hemochromatosis by activation of the hemojuvelin gene.[15] Furin is highly expressed in the Golgi apparatus where it cleaves inactive proteins to their active forms.[15] Furin is also concerned in the activation of virus envelop proteins as in human immune deficiency virus, dengue fever, influenza virus, Ebola virus, Marburg virus, and severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).[16] Furin is also engaged in the proteolytic activation of pseudomonas and anthrax toxins.[14,17]

Variations and defects in the expression and enzyme activity of furin promote the progression of a wide range of diseases including dementia, rheumatoid arthritis, and cancer.[18,19] Moreover, furin has a role in the activation differentiation and growth of human cells.[19] Aberrant activation of furin promotes abnormal cell proliferation and the development of cancer. PC furin increases the pathogenesis of viral and bacterial infections (Figure 1).

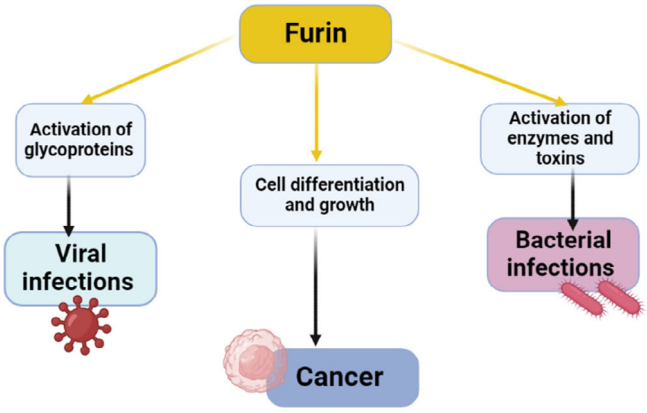

FIGURE 1 Role of proprotein convertase furin in the development of cancer and viral/bacterial infections.

3 | FURIN AND CARDIOMETABOLIC DISORDERS

It has been shown that furin is associated with development of cardiometabolic disorders including obesity and type 2 diabetes mellitus (T2DM).[20,21] Furin enhances the levels of high-density lipoprotein by deactivating lipoprotein lipases in the endothelium.[22] The cleavage of membrane-bound transcription factors, specifically referred to as sterol regulatory element binding proteins, by furin leads to the increase in the synthesis of sterols, lipids, and the LDL receptor.[22] Furin is responsible for the reduction of protein levels of the LDL receptor by amplifying its intracellular metabolic pathway in acidic compartments within the subcellular environment.[22] Furthermore, hepatic furin diminishes the functionality of endothelial lipase by means of stimulating the cleavage of angiopoietin-like protein 3, which is an innate inhibitor of endothelial lipase.[23] Therefore, the act of inhibiting furin in the liver leads to an increase in the activity of endothelial lipase, which subsequently causes a reduction in HDL-C levels and hampers the process of reverse cholesterol transport.[23] The hepatic furin pathway represents a newly discovered mechanism that controls the metabolism of high-density lipoproteins (HDL) and the maintenance of cholesterol homeostasis.[23] The results of this study imply that furin plays a role in lipid metabolism and the development of dyslipidemia.

A population-based prospective study involved subjects at high risk for the development of T2DM and revealed that initial high furin serum levels increased the risk for the development of T2DM and premature mortality.[20,24] Mutation in furin induces propagation of insulin resistance (IR) and T2DM due to association with mutation in the insulin pro-receptors.[25] Indeed, high circulating furin serum level is correlated with dyslipidemia, high body mass index, and development of metabolic syndrome.[26] Moreover, genetic variation of furin is connected with the development of systemic hypertension.[27] A cohort study that included 94 hypertensive patients showed that single nucleotide polymorphism of furin was associated with the development and severity of hypertension.[27]

In contrast, a longitudinal study comprised Chinese adults with hypertension illustrated that low furin levels were associated with a high risk of hypertension[28] suggesting a protective effect of furin. Similarly, a prospective study demonstrated that a deficiency of furin increases the risk for the development of abdominal obesity.[29–31] However, Ren et al.[32] disclosed that furin through induction of inflammatory reaction and lipid dysmetabolism may promote the propagation of atherosclerosis and hypertension. These findings suggest a latent controversy regarding the role of furin in the development of cardiometabolic disorders. Recently, cardiometabolic disorders have been associated with the development and progression of different cancer types including EAC.[33] It has been observed that obesity is regarded as an established risk factor for EAC, and weight reduction in obese women by bariatric surgery decreases EAC risk by 81%.[34] In addition, the use of combined oral contraceptives protects against EAC for about 30 years.[34] The mechanisms of obesity-induced EAC are not fully elucidated, though adipose-derived estrogen, which is unopposed by progesterone in postmenopausal obese women could be the potential mechanism.[35] Besides, T2DM and IR promote the development of EAC due to dysregulation of insulin signaling and adipocytokines.[36] However, a systematic review and meta-analysis illustrated that insulin-sensitizing metformin improves survival in patients with EAC, but does not prevent endometrial proliferation after 2–16 weeks of treatment.[37] Furthermore, hormonal changes are increased at menopause characterized by reducing estrogen levels, which cause loss of subcutaneous adipose tissue and augment visceral fat.[38,39] However, adipose tissues remain the major source of estrogen by converting androgen derived from ovary and adrenal gland to estrogen via aromatase enzyme, which is highly expressed in adipose tissue.[38,39] Therefore, hormonal changes in menopause and the development of visceral obesity together with cardiometabolic may increase EAC through furin-dependent mechanisms.

4 | FURIN AND TUMOR PROGRESSION

Furin is considered a master switch and regulator of tumor cell proliferation and progression.[40] The expression of aberrant furin triggers the development and progression of different types of malignancies including lung carcinoma, rhabdomyosarcoma, colonic cancer, and skin cancers.[10,40] It has been reported that furin was regarded as a potential biomarker of cancer staging since it correlated with the aggressiveness of cancer type.[40] Furin promotes angiogenesis, malignant cell proliferation, and tissue invasion by malignant cells through its pro-metastatic and oncogenic activities.[40] In addition, furin through activation of numerous growth factors increases cell proliferation and tumor growth.[10,40] For example, furin promotes the activation of vascular endothelial growth factor and lymphangiogenic factor which increase the vascularization of solid tumors.[40]

Of note, furin also increases the proliferation and vascularization of tumors in hypoxic areas. Tissue hypoxia induces the expression of hypoxia-inducible factor 1 alpha, which triggers the induction of furin in hypoxic tissues.[41] Also, hypoxia enhances intracellular localization of furin with subsequent direct interaction and activation of oncogenic growth factors.[41] Thus, hypoxia may increase the proliferation and growth of malignant cells through the furin-dependent pathway.

Furthermore, furin can increase metastasis of malignant cells through induction the expression of integrin and matrix metalloproteinases (MMPs), which assist metastasis by degrading the extracellular matrix.[42] Notably, there is a close interaction between furin and interferon-gamma (INF-γ), which increase the expression of PC furin. Castro et al.[43] pointed out that INF-γ may have a pro-tumorigenic role through the downregulation expression of major histocompatibility complexes, also it acts as a checkpoint inhibitor promoting immunosuppressive microenvironment in the tumor area. Furthermore, furin increases the expression of INF-γ during tumor growth and invasion.[44]

Interestingly, furin attenuates cell antitumor activity by promoting the development of immunotolerant and immunosuppressive T cells namely regulatory T cells with inhibition of cytotoxic T cells.[45] Besides, activated immune cells as activated T cells demonstrated a

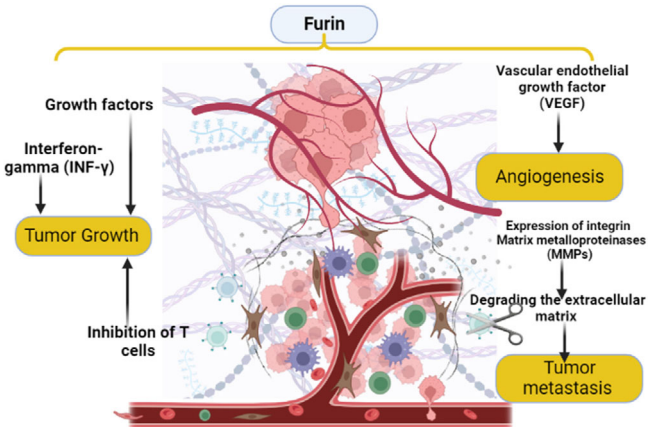

FIGURE 2 The role of furin in tumor progression: furin activates expression of growth factors which stimulate cell proliferation; furin increases metastasis by increasing the expression of integrin and matrix metalloproteinases (MMPs), also furin reduces cellular antitumor activity by inhibition of T cells. These changes trigger tumor progression.

higher expression of furin.[45] As well, infiltration of tumors by the immune cells is correlated with the expression of furin. In this state, deficiency of furin may be associated with the reduction in the infiltration of the tumor by immunosuppressive regulatory T cells leading to a better immunological response.[45,46] Herein, the inactivation of furin in the activated T cells may inhibit tumor growth and invasion.[46] Therefore, targeting furin could be a potential therapeutic value in the management of cancer.[40] However, PC furin inhibitors may increase the aggressiveness of some human cancers.[40]

In vitro study, included ovarian cancer cell lines demonstrated that furin was highly expressed[47] suggesting that furin could be a biomarker of ovarian carcinoma.[47] Chen and colleagues observed that furin induces proliferation and metastasis of ovarian cancer through stimulation of signal transducer activator transduction 3.[48,49] Moreover, in vitro and in vivo studies revealed that overexpression of furin was correlated with the risk of cancer development.[50,51]

Moreover, furin activity is increased in both atypical endometrial hyperplasia and endometriosis.[10,30] Total furin activity in cervical swabs and uterine lavage correlated with the severity and progression of atypical endometrial hyperplasia and endometriosis.[10,30] An experimental study illustrated that inhibition growth of endometriosis by baicalein reduced furin level.[52] The results imply the possible function of PC furin in the propagation of atypical endometrial hyperplasia and endometriosis.

These verdicts proposed that aberrant activation of furin is correlated with malignant proliferation and metastasis of different mammalian cancers (Figure 2).

5 | FURIN AND EAC

Low-grade EAC is characterized by well-differentiated cells not invading the myometrium.[1] However, high-grade EAC is less differentiated and associated with atrophied endometrium.[3] Some EAC have many foci of mucinous changes, which increase the severity and invasiveness of EAC.[1,3] Of note, furin activity is correlated with the malignant proliferation of EAC.[10] A direct link between furin activity and the development of EAC was less assessed in the clinical studies. However, a recent study confirmed the association between a higher expression of TGF-β and the progression of EAC.[53] Particularly, furin is regarded as a TGF-β converting enzyme that increase the oncogenic activity of TGF-β.[54] In addition, plasminogen activator inhibitor 1 (PAI-1) inhibits intracellular activation of furin thereby reducing derangement in metabolic syndrome.[55,56] Therefore, PAI-1 attenuates intracellular communication of adiposity-mediated development of EAC through inhibition of PC furin.[57] Besides, PAI-1 inhibits the expression of TGF-β.[57] Thus, a higher expression of PAI-1 in obesity could be a protective mechanism against the development of EAC through suppression of furin/TGF-β axis.[58]

Furthermore, furin induces the processing of CD109 into small proteins which form an intricate complex with type 1 TGF-β receptor for the direction of TGF-β signaling in cancer cells.[59] It has been reported that expression of the CD109 gene was increased in patients with EAC, though this expression was higher in cervical squamous cell carcinoma compared to EAC.[60] In general, the expression of the CD109 gene was elevated mainly in squamous cell carcinoma than in adenocarcinoma.[61] A meta-analysis study illustrated that the expression of the CD109 gene could be a beneficial biomarker of cancer in general.[62] These observations suggest that the CD109 gene is not a specific biomarker in women with EAC.

Moreover, emerging evidence proposes a potential role of the pro-renin receptor in the ontogenesis and pathogenesis of EAC. In vitro study used endometrial cancer cell lines demonstrated that the pro-renin receptor was crucial for the development of EAC through maintaining endometrial cell viability.[63] As well, the pro-renin receptor is highly expressed in human EAC compared to normal endometrium.[63] Pro-renin receptor improves cell migration, proliferation, and angiogenesis, which are essential for tumorigenesis of EAC.[64] Pro-renin receptor promotes activation of the renin-angiotensin system (RAS), increasing the production of angiotensin II.[65,66] Similarly, the pro-renin receptor enhances cellular viability and proliferation through induction expression of growth factors like phosphatidylinositol 3 kinase p85α subunit (PI3K-p85α).[65,67–69] Pringle et al.[70] study demonstrated that women with EAC had mutant RAS compared to healthy women. Obesity and high estrogen level are implicated in the generation of mutant RAS with the development of EAC.[70] Therefore, RAS inhibitors could be protective agents against the development of cancer in both males and females by inhibiting RAS/pro-renin receptor axis-mediated intracellular activation.[71,72] In this state, furin increases the activity and level of the soluble pro-renin receptor by intracellular cleavage.[73]

Indeed, disintegrin and metalloprotease 17 (ADAM17) also increase proteolytic activation of pro-renin receptor.[73] ADAM17-mediated proteolysis of membrane proteins promotes intracellular signal transduction in cell proliferation, migration, and differentiation.[74] ADAM17 increases the release of tumor necrosis factor-alpha (TNF-α) with induction of

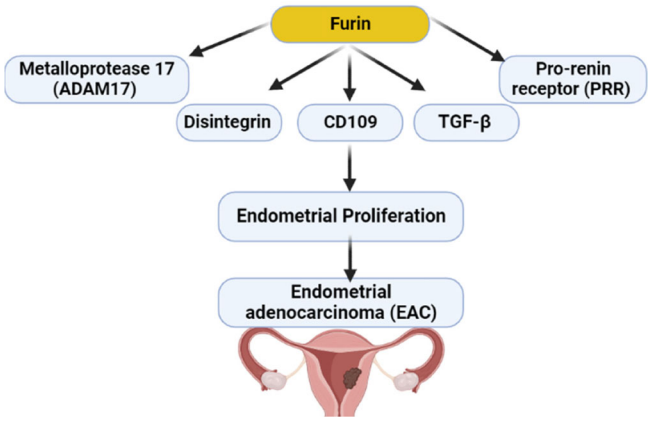

FIGURE 3 Role of furin in the development of endometrial adenocarcinoma (EAC): furin activates expression of transforming growth factor-beta (TGF-β), CD109, pro-renin receptor (PRR) and disintegrin and metalloprotease 17 (ADAM17) with subsequent endometrial proliferation and EAC.

inflammation.[24,75,76] ADAM17 is activated by PC furin with subsequent induction release of TNF-α.[75] Higher ADAM17 expression is linked with the development of EAC.[77] Xu and coworkers found that a high level of ADAM17 was associated with poor clinical outcomes in women with uterine carcinoma.[78] Therefore, higher expression of furin may increase the development of EAC through overexpression of pro-renin receptors and ADAM17 (Figure 3).

Expression of furin was increased in postmenopausal endometrial biopsies as compared to controls.[11] Uterine lavage is a noninvasive source material for evaluating the endometrium. Furin activity was altered in the uterine lavage of EAC patients as compared to controls.[11] Furin activity was detected in all uterine lavage samples and significantly elevated in all grades of EAC.[11] Notably, the expression of furin is variable according to the stages of EAC, being higher in the early stages and reduced with increasing grades of EAC.[11] Endometrial biopsies from 30 women with EAC and 7 healthy controls showed that furin activity was higher in patients compared to controls, but this expression was reduced as the disease advanced.[11] However, total PC activity of uterine lavage was increased in all grades and stages of EAC in women with EAC compared with healthy controls.[11] These findings suggest that furin is more accurate than total PC in the diagnosis, staging, and prognosis of EAC, as a furin decrease indicates a poor prognosis.

Thus, monitoring the total PC activity in uterine lavage may provide a rapid and noninvasive method for the diagnosis of EAC in postmenopausal women.[11] Heng et al.[30] observed that furin activity was significantly increased in the uterine lavage of postmenopausal women with EAC. Uterine lavage can be acquired in a noninvasive manner in contrast to the procurement of uterine tissues; nonetheless, the broad clinical application of uterine lavage is constrained by blood contamination and various other factors. The correlation between furin activity in swabs and lavage was found to be remarkably significant in postmenopausal women. Moreover, there was a notable increase in furin activity within endocervical swabs in patients with EAC as compared to the control group.[30] Hence, the furin activity observed in endocervical swabs could potentially serve as a straightforward, nonintrusive, and innovative approach for identifying EAC in women who have reached menopause.

6 | FURIN AND INFLAMMATION IN EAC

It has been shown that furin has pro-inflammatory and anti-inflammatory effects in different inflammatory and metabolic disorders.[79] Furin level is correlated with the level of pro-inflammatory cytokines.[79,80] A comparative study illustrated that children with obesity had a higher rate of furin and pro-inflammatory cytokine levels as compared to normal-weight children.[79] Inhibition of furin was shown to decrease vascular remodeling and systemic inflammation.[81,82] Therefore, a high furin level reflects underlying systemic inflammation and could be a potential link between obesity and inflammation.

In contrast, a previous study demonstrated that myeloid cells expressing furin had anti-inflammatory effects through modulation of T cell immune response and tolerance.[83,84] Experimental studies revealed that deletion of furin promotes aberrant activation and polarization of T cells with the development of autoimmunity due to the lack of immune tolerance.[85,86] Lin et al.[87] illustrated that furin had a protective role against inflammatory changes in patients with rheumatoid arthritis by regulating T cell immune tolerance. These verdicts suggest a pro-inflammatory and anti-inflammatory role of furin in different inflammatory conditions.

On the other hand, it has been hypothesized that chronic inflammation may promote the development of EAC through induction of rapid cell division; DNA injury; mutation and ineffective DNA repair.[2,88] High estrogen improves endometrial inflammation through the induction expression of prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2), which induce tumorigenesis by increasing the generation of pro-inflammatory cytokines including interleukin (IL)-6 and IL-8.[89,90] Besides, COX-2 increases the generation of free radicals and reactive oxygen species (ROS) through the induction expression of nitric oxide synthase.[89,91] Thus, ROS and inflammatory reactions in the endometrium may induce neoplastic transformation and the development of EAC.[88]

Indeed, the inflammatory signaling pathway nuclear factor kappa B (NF-κB) is involved in cell proliferation, apoptosis, and angiogenesis. NF-κB provokes malignancy signaling in both tumor-associated inflammatory and cancer cells.[92,93] Inhibition of the NF-κB signaling pathway and associated inflammatory changes may decrease the risk of malignant transformation and progression of EAC.[94] Of note, furin increases the expression of COX-2, PGE2, and NF-κB in the initiation of labor.[95] Also, PGE2 and COX-2 increase the expression of furin, and inhibition of COX-2 and PGE2 can decrease the expression of PC furin in cancer cells.[95] Interestingly, activated NF-κB promotes the expression of furin in EAC.[96] Therefore, nonsteroidal anti-inflammatory drugs like aspirin could be effective in reducing the risk of EAC through inhibition of the NF-κB/COX-2 axis.[97,98] A meta-analysis included seven case–control studies and eleventh cohort

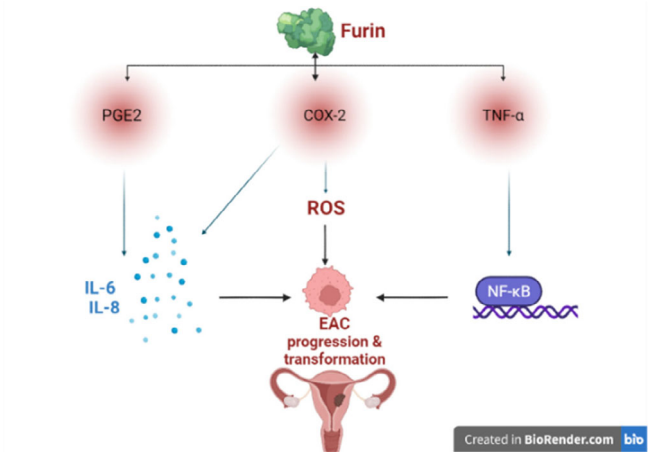

FIGURE 4 Inflammatory signaling in endometrial adenocarcinoma (EAC): EAC promotes the expression of proprotein convertase furin with further propagation of malignant transformation. COX-2, cyclooxygenase-2; NF-κB, nuclear factor kappa B; PGE2, prostaglandin E2; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

studies of 14 766 endometrial cases showed that aspirin was regarded as a protective factor against the development of EAC.[99]

These findings suggest that inflammatory signaling in EAC promotes the expression of furin with further propagation of malignant transformation (Figure 4).

7 | FURIN INHIBITORS

Expression and activity of furin are essential for tumor progression and metastasis via activation of MMPs, which are correlated with tumor aggressiveness.[100] Furin inhibitors could be of therapeutic value in inflammation, infection, and cancer.[101] It has been reported that polyarginines are potent furin inhibitors.[101] Small molecule compounds that inhibit furin and/or furin are of great value in cancer management.[100] In vitro and vivo findings showed that furin inhibitor alpha-1PDX reduced tumorigenicity in a considerable way.[100] Despite evidence of efficacy in preclinical studies, no furin inhibitor is used clinically. Therefore, repurposing clinically FDA-approved furin inhibitors is of great value.

7.1 | Metformin

Insulin-sensitizing drug metformin had been confirmed by preclinical in vitro study to inhibit furin and other genes associated with tumor progression and invasion.[102] Of interest, in vitro invasion in EAC was considerably inhibited by sera from women with polycystic ovarian syndrome following 6 months of metformin treatment.[103] This effect is mediated by the inhibition of MMP-2/9 and furin.[103] Other studies also confirmed the effectiveness of metformin against EAC.[104–107] In addition, metformin reverses obesity-induced aggressiveness of EAC by inhibiting growth factors.[108] It has been shown that metformin the proliferation of EAC as documented in an in vitro study in a dose-dependent manner in progesterone resistance Ishikawa cells by inducing autophagy[108] signifying that metformin is effective in progesterone resistance EAC. A randomized clinical trial started in 2019, showed that medroxyprogesterone acetate in combination with metformin is an effective therapeutic strategy against EAC.[105] A systematic review and meta-analysis showed that metformin in combination with progestin is more effective than progestin alone in the management of atypical endometrial hyperplasia and early EAC.[109] Metformin can mitigate abnormal glucose metabolism, IR, and hyperinsulinemia, which are involved in the pathogenesis of EAC.[105] In addition, medroxyprogesterone antagonizes the carcinogenic effect of estrogen,[105] therefore this combination seems to be more appropriate in postmenopausal women with obesity and EAC. A clinical trial showed that long-term metformin treatment can induce endometrial atrophy in 96% of women with endometrial hyperplasia.[110] The anticancer mechanism is mediated by inhibiting inflammatory signaling pathways, such as mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK), which are involved in the pathogenesis of EAC.[106] A case–control study revealed that metformin inhibits the AKT/PI3K/mTOR signaling pathway in women with EAC compared to healthy controls.[107] These findings indicated that metformin through inhibition of furin, inflammatory signaling pathways, and growth factors may be effective in treating EAC.

7.2 | Statins

Statins are 3-hydroxyl-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibit hepatic denovo cholesterol biosynthesis.[111,112] Statins are widely used in the management of hypercholesterolemia and dyslipidemia, therefore they are used in the prevention of primary and secondary cardiovascular complications. In addition, statins have anti-inflammatory, antioxidant, anti-thrombotic, and antiapoptotic effects.[113] Moreover, clinical studies established that statins have the ability to inhibit furin activity.[114,115] Furin plasma levels are increased in patients with acute cardiac events and following cardiac intervention in statins-free patients but reduced in statins-treated patients.[106,114] Higher plasma levels of furin and PCSK9 in patients with acute cardiac events are associated with resistance to statins therapy.[115] In addition, statins attenuate SARS-CoV-2 infection by inhibiting furin.[116] Interestingly, high cholesterol increases the activity of furin for priming and activation of SARS-CoV-2 spike protein to bind angiotensin-converting enzyme 2 (ACE2).[117] Therefore, statins can directly inhibit furin or indirectly reduce furin activity by reducing cholesterol.

On the other hand, statins can improve the survival of women patients with EAC by inhibiting endometrial cell proliferation and migration through modulation of the expression of furin.[118,119] However, long-term use of statins led to borderline or ineffectiveness against the development and progression of EAC.[120] Statins have chemoprotective effects against EAC in high-risk group women.[118] Findings from the Australian record linkage study demonstrated a

potential benefit for statins use in women with EAC.[119] It has been reported women with EAC on statins therapy had a lower mortality rate compared to women not on statins therapy.[119] A retrospective study involved 985 women with EAC showed that statins improved survival and reduce complications.[121] In many epidemiological studies statins reduced EAC and ovarian risk,[122] however, statins were reported to be effective for ovarian but not for EAC.[123] However, a meta-analysis and systematic review revealed that long-term use of statins >5 years did not EAC risk.[124] These findings suggest that statins via inhibition of furin could be effective as adjuvant treatments in the management of EAC.

7.3 | Baicalein

Baicalein is a flavonoid isolated from *Scutellaria lateriflora* and *Scutellaria balacalensis*, has anti-inflammatory, antioxidant, and anticancer effects.[125] Baicalein is regarded as an allosteric modulator of benzodiazepine receptors, and inhibits lipooxygenase.[126] It has been observed that baicalein has anticancer properties by numerous molecular mechanisms including inhibition of PI3K/AKT/mTOR, and MAPK.[127] Furthermore, baicalein inhibits adenosine diphosphate ribosylation factor 6, which promotes the proliferation and invasion of endometrial cancer cells.[128] Similarly, baicalein modulates the expression of progesterone receptors, which is intricate in the development of EAC.[129] Furthermore, baicalein attenuates the carcinogenesis of EAC by inhibiting the expression of inflammatory signaling pathways.[130] As baicalein is not clinically approved, therefore there are limitations regarding the clinical effects of baicalein in women with EAC.

The underlying mechanism of baicalein in suppressing proliferation and invasion of EAC is not fully elucidated. However, inhibition of endometrial furin by baicalein could a possible mechanism. Preclinical studies illustrated that baicalein can inhibit endometrial proliferation and ectopic endometriosis by inducing apoptosis and expression of MMP and furin.[52,131] Therefore, furin inhibitor baicalein according to the preclinical findings seems to be effective against EAC.

Taken together, furin inhibitors, such as metformin and statins could be a novel adjuvant therapeutic strategy in the management of EAC.

The present review had several limitations including a paucity of clinical studies and the sequential level of furin in the different stages of EAC was not reviewed. However, this review highlighted the potential role of furin and associated inflammatory changes in the propagation of EAC. These findings indicated that furin inhibitors produce borderline effects in EAC. Therefore, this review exciting researchers in this field to perform future clinical trials, pilot, and prospective studies to confirm the exact role of furin in the pathogenesis of EAC regarding the efficacy and safety of furin inhibtors.

8 | CONCLUSIONS

EAC is the most common malignant tumor of the female genital tract and is linked with menopause, obesity, and other cardiometabolic disorders. Furin is associated with the development and progression of EAC through induction of proliferation, invasion, and metastasis of malignant cells of EAC. Furin induces EAC through activation expression of ADAM17, pro-renin receptor, CD109, and TGF-β. As well, EAC-mediated inflammation promotes expression of furin with further propagation of neoplastic growth and invasion. Taken together, furin has direct and indirect role in the advancement of EAC. Therefore, experimental and clinical studies are reasonable in this state to verify the potential role of furin in the development of EAC.

AUTHOR CONTRIBUTIONS

Hayder M. Al-kuraishy, Thabat J. Al-Maiahy, Ali I. Al-Gareeb, Athanasios Alexiou: Conceptualization (lead); visualization; writing—original draft (lead). **Marios Papadakis**: writing—original draft (lead); funding acquisition (lead). **Hebatallah M. Saad, Gaber El-Saber Batiha**: Conceptualization; supervision; resources (lead); writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Not applicable.

CONSENT FOR PUBLICATION

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