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p27^{kip1} as a Key Regulator of Endometriosis

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Abstract

Endometriosis is a gynecological benign chronic disease defined as the growth of endometrial glands and stroma in extra-uterine sites, most commonly implanted over visceral and peritoneal surfaces within the female pelvis causing inflammatory lesions. It affects around 10% of the female population and is often accompanied by chronic pelvic pain, adhesion formation and infertility. The expression of cell cycle and inflammatory proteins is modified in the endometriotic tissues. Immunostaining of glandular and stromal cells in endometrial biopsies obtained from patients with endometriosis compared with those of healthy control demonstrated that endometriotic tissues have lower levels of p27^{kip1} protein. Endometriosis endometrial cells cultures have also lower levels of p27^{kip1} compared to health endometrial cells cultures and restore the cell cycle balance when transduced with an adenoviral vector caring the p27^{kip1} coding gene (Adp27EGFP). The low levels of p27^{kip1} are related to the S phase in the cell cycle, whereas higher levels lead to a G1 cell cycle arrest. The goal of this highlight review is to provide a broad overview of the advancements in endometriosis mainly correlating the cytokine p27^{kip1} expression with the disease regulation. This review is a synopsis of important findings for researchers to quickly and relevant sources of interest to his/her studies.

Keywords: p27^{kip1}; Endometriosis; Endometrium disorders

Introduction

Endometriosis is a complex gynecologic disease characterized by the presence of functional endometrial-like tissues at sites outside of the uterine cavity. It is present in about 10% of women [1], it is highly prevalent in infertile patients (50%) [2] and also in women with chronic pelvic pain (15 to 80%). Lesions identified during laparoscopy are categorized as superficial peritoneal lesions, endometriomas, or deep infiltrating nodules, with high degree of individual variability in lesion color, size, and morphology. Histopathological analysis requires the presence of at least two features for a diagnosis of endometriosis, the features being endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-filled macrophages [3].

Retrograde menstruation, in which uterine epithelial and stromal cells are disseminated and implanted into the peritoneal cavity via the fallopian tubes, is the most accepted mechanism for the pathogenesis of endometriosis [4]. More than 90% of women undergo retrograde menstruation; however, the prevalence of endometriosis in the general population is 6–10% [5,6]. Such a discrepancy between these two values suggests that women who develop endometriosis are likely to have other genetic, biochemical, and pathophysiological factors contributing to development of the disease [7].

Pain and infertility are two prominent symptoms most commonly associated with the endometriosis and have been attributed to chronic inflammatory state of the pelvic peritoneal area with altered immunological and inflammatory milieu in the microenvironment [8]. This is can be deduced by two main features found in the peritoneal environment, the increase in immune cells and the elevation of pro-inflammatory immunomodulatory proteins (cytokines and chemokines) and lipid mediators such as prostaglandins in the peritoneum and peritoneal fluids of women with endometriosis [9].

Endometriosis establishment requires the implantation and survival of endometrial cells outside of uterus, which is supposed to be a polygenic inherited disease with multifactorial etiology related to genetic, immunologic, hormonal and environmental factors [10-12]. Molecular disorders in the topic endometrium from women with endometriosis, such as escape from apoptosis, degradation of extracellular matrix, invasion, recruitment of inflammatory cells, acquisition of steroidogenic capacity, evasion from immune system and enhanced angiogenesis capacity have already been established [13-16].

Several factors, such as increased of inflammatory activity in the peritoneal fluid, angiogenesis and up-regulating of pro-inflammatory cytokines may facilitate the pathogenesis of endometriosis, which is assumed to be a complex process [17].

One important cytokine enrolled with endometriosis development is the p27^{kip1}. The critical function of p27^{kip1} is to inhibit CDK-cyclin E complex by controlling a checkpoint in the G1 in normal cells. When p27^{kip1} is not present in the cells, cells are not follow a cell cycle control signal and proliferation. Because endometrial cell cycle changes may be involved in cell cycle regulation of endometriosis in women with diseases significance of p27^{kip1} protein level it can be seen that a change in the lining of a particular cell cycle is important [18].

The goal of this review is to provide a broad overview of the advancements in endometriosis mainly correlating the cytokine p27^{kip1} expression with the disease regulation. This review is a synopsis of important findings for researchers to quickly and relevant sources of interest to his/her studies.

p27^{kip1} Structure and Function

The critical function of p27^{kip1} is to inhibit CDK-cyclin E complex

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by controlling a checkpoint in the G1 in normal cells. When $p27^{kip1}$ is not present in the cells, cells are not follow a cell cycle control signal and proliferation [19]. Because endometrial cell cycle changes may be involved in cell cycle regulation of endometriosis in women with diseases significance of $p27^{kip1}$ protein level it can be seen that a change in the lining of a particular cell cycle is important [20].

Due to capacity of endometrial cells implant and survive in ectopic sites, apoptosis and cell cycle disruptions have been always investigated. Molecules involved in apoptosis and cell cycle control as Bcl_2, p53, Bak, Ki67, telomerase, PCNA, Pak-I, ERK1/2, c-myc and $p27^{Kip1}$ may therefore be critical features in endometriosis [21]. The $p27^{kip1}$ protein performs a fundamental role in cell cycle regulation, controlling the G1 to S phase transition, called checkpoint [22,23] binding to numerous cyclin / CDK (cyclin-dependent kinases) complexes throughout the cell cycle, and it is one exemplary CDK inhibitor, whose misregulation is found in various cancer types [24-27]. The $p27^{kip1}$ protein was first identified as an inhibitor of cyclin E/CDK2 complexes during TGFβ-induced G1 arrest, and CDK inhibitors are often associated with pathological conditions when mutated, up- or down-regulated. The expression of $p27^{kip1}$ not only bears a significant relation to cellular differentiation, but when linked to cyclin E/CDK2, also prevents the cell cycle from starting in the absence of external stimulus [28]. A major regulatory mechanism of controlling the $p27^{kip1}$ inhibitory function is to regulate $p27^{kip1}$ protein levels through transcriptional, translational, and post-translational mechanisms [29-31].

$p27^{kip1}$ and Endometriosis

Previous studies of cellular proliferation and apoptosis in endometriosis have not reached a consensus regarding the proliferation indices of stromal or glandular cells, nor have they settled on the phase of the menstrual cycle at which alterations would be more evident [32-35] demonstrated a significant decrease in the levels of p27 protein in the epithelium and stroma in the second phase of the cycle in women with endometriosis. These data indicate an alteration in the cell cycle of endometrial cells and suggest alteration of a signaling pathway. Decreased levels of this protein, in both the epithelium and the stroma, in endometriosis suggests that various cell types are involved in the genesis of the disease. These results corroborate an earlier report by [36] which found that expression of c-Myc, transforming growth factor β1, and Bax genes resulted in a significant increase in the proliferation index of endometrial epithelia of women with endometriosis. This study was the first one to emphasize an alteration in the expression of a specific cell cycle regulatory protein, which suggested a signaling pathway that may be altered in endometriosis. This alteration was observed in the multiple stages of the disease, suggesting that it may be an initiation factor and that progression of the disease to advanced stages is probably due to other factors.

One of the critical steps around endometriosis pathogenesis is an active angiogenic process [37], highlighted by increased levels of growth factors in peritoneal fluid [38] and angiogenic potential of eutopic endometrium [15]. Thus, an intricate network of host angiogenic and immune responses are activated in pelvis of endometriosis patients, which allow the implanting and growing of ectopic endometrial cell. However, the molecular process of angiogenic activation is still unclear.

VEGF is a secreted heparin-binding homodymeric glycoprotein of z 46kD, with several protein variants resulting from alternative splicing of VEGF mRNA [39,40]. It action is triggered by tyrosine kinase receptors, fms-like tyrosine kinase (flt) or kinase domain receptor (KDR), present predominately on endothelial cells [41]. The VEGF is not only a potent endothelial cell mitogen, morphogen, and vascular permeability–inducing agent, but it activation also leads to the expression of a number of proteolytic enzymes involved in the process of angiogenesis [42]. VEGF is expressed by eutopic endometrium [43], and is overexpressed in peritoneal fluid from endometriosis patients [44] which can contribute to the development of vasculature and the subsequent maintenance of endometriotic explants [23].

Members of the Cip/Kip family of cyclin-dependent kinase inhibitors are well characterized for their roles as negative regulators in the G1-phase cell cycle progression. However, emerging studies suggest that $p27^{kip1}$ play roles additional to cell cycle controls [18,45].

$p27^{kip1}$ as a Key Regulator

Studies showing the high proliferation rates and lower expression levels of $p27^{kip1}$ in eutopic endometrial cells suggest that $p27^{kip1}$ maybe take part in this cell cycle disorder [35,46-48]. Both the processes, diminished $p27^{kip1}$ and enhanced VEGF expression and previous studies in animal prompted us to investigate the relationship between $p27^{kip1}$ expression and VEGF synthesis by primary endometrial cells cultures from endometriosis patients. We firstly observed that primary culture cells from eutopic endometrium in endometriosis patients express higher basal levels of VEGF. Then, we demonstrated that overexpression of $p27^{kip1}$ in endometrial cells from women with endometriosis is able to regulate the VEGF expression to levels closely to those observed in women without endometriosis.

The expressions of a wide array of cytokines are abnormal in the processes of tumor invasion and metastasis as well as in endometriosis [49]. Among them, VEGF and MMP-9 play important roles in the processes. Progression of malignant tumor is characterized by the formation of new vessels and the newly formed vessels act as a bridge between tumor and circulation system, which facilitate the metastasis of cancer cells to distant parts of body. The formation of new vessels entails participation of a good many cytokines and among them, VEGF is believed to be the most potent vessel-forming factor. Chen revealed in their study that Ad-p27 could inhibit the expression of VEGF and thereby suppressed the generation of tumor-feeding vessels and stopped the growth of tumors [50].

In vitro study demonstrated the MIF, VEGF and $p27^{Kip1}$ are molecules involved in a network of inflammatory and angiogenic systems [51], but mechanisms of regulation remain unclear. Also, down-regulation of $p27^{Kip1}$ appears to be early event in endometriosis and may be important for the establishment of the endometriotic implants [47].

The expression of $p27^{kip1}$ is subject to multiple mechanisms of control involving several transcription factors, kinase pathways and at least three different ubiquitin ligases, which regulate $p27^{kip1}$ transcription, translation, protein stability and subcellular localization [52]. We observed the control group also showed a small

decrease of VEGF after $p27^{Kip1}$ transduction, while that difference on endometriosis cells presented a higher range. On the other hand, the longitudinal analysis showed the modification of VEGF levels according to culture time was not significant in control group. Those results suggest $p27^{kip1}$ regulation is not affected on control cells.

In women with endometriosis, the peritoneal fluid has high concentrations of cytokines, growth factors, and angiogenic factors [1], derived from the lesions themselves; secretory products of macrophages and other immune cells; and follicular fluid after follicle rupture in ovulating women. Once endometriotic lesions are formed, they secrete several pro-inflammatory molecules [53]. IL-1β has been suggested to support the development of endometriosis through the production of various inflammatory molecules including IL-6, IL-8, MCP-1 and COX-2 [54]. The present finding raises a novel notion that IL-1β may promote the disease through the microenvironment with stem cell. The presence of stem progenitor cells in endometrium and in menstrual blood led to the hypothesis that these cells could be at least in part responsible for the development of endometriosis. Lots of studies in the last decade have contributed to the consolidation of this hypothesis, through different approaches [55]. In one study, it was suggested that the basal layer of endometrium was significantly shed in menstrual flow in women with endometriosis, in comparison with control women [56]. Interestingly, endometrial stem cells are particularly frequent in endometrial tissue during menstruation. It has been speculated that endometrial stem cells may play an important role in the development of endometrial implants [57,58] demonstrated that adiponectin induces cell cycle arrest in certain cancer cell lines such as hepatoma HepG2, prostate carcinoma PC-3, and breast cancer MCF-7 by upregulating tumor suppressor genes such as p53, p21, and p27 [59-61]. Also, it has been demonstrated that these effects on cancer cell proliferation are associated with decreased expression of cyclins and increased expression of p27 [62,63]. Recently, we demonstrated that an increase in $p27^{kip1}$ expression leads to a decrease in IL-1ß expression [64].

Considerations and Perspectives

A strong reduction in the tumor suppressor gene $p27^{kip1}$ results in a high resistance and poor prognosis in cancer. Also $p27^{kip1}$ has an important role cell cycle regulatory factor. Recently, $p27^{kip1}$ has been reported that many women involved in diseases such as breast cancer, endometriosis and ovarian cancer.

Further studies strongly demonstrate the role of $p27^{kip1}$ as a key factor in regulating progression of endometriosis because those findings, in the future, might open up interesting perspectives for the use of $p27^{kip1}$ targeted gene therapy as an alternative or additional strategy in the treatment of endometriosis.

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