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Review Article

## Mechanism of Immune System Dysfunction, Apoptosis and Oxidative Stress on Endometriosis

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### Abstract

Endometriosis is a gynecological disease that still requires advanced knowledge to develop the best treatment to improve the patient's best quality of life. It is characterized by the formation of endometrial tissue outside the uterus and occurs approximately in 5-10% of women of childbearing age. Endometriosis with poor prognosis can be at high risk of endometrial cancer, ovarian cancer and lead to infertility. In-depth efforts are needed to achieve a clear knowledge of the molecular etiology of endometriosis. Here, there are three dysfunctional molecular mechanism that occur in endometriosis; (1) immune system dysfunction, (2) impaired apoptotic signaling, (3) and increased oxidative stress. These three dysfunctional molecular mechanisms are thought to promote endometriosis development and worse prognosis. Therefore, determining the molecular pathogenesis of endometriosis will be useful in the development of diagnostic and therapeutic methods.

**Keywords:** *Endometriosis; Immune Dysfunction; Apoptosis; Oxidative Stress*

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### INTRODUCTION

Endometriosis is a chronic inflammation disease. The most symptom is pelvic pain, occurring in 75% of endometriosis women.<sup>1</sup> Approximately 30-50% women with endometriosis having infertility and women with endometriosis have high risk to be infertile.<sup>2</sup> Determining the molecular mechanism that occurs in endometriosis is needed for better knowledge regarding diagnostic and therapeutic methods of endometriosis. It has been reported that estrogen level increased in women with endometriosis; additionally genetic factor, endocrine, lifestyle, and immune system dysfunction are also contributing to endometriosis etiology. The appearance of endometrium tissue outside the uterus is reported due to the releasing of endometrium cells, then migrate to the pelvic through the fallopian tube during menstrual.<sup>3</sup> The released endometrial cells can bind also to several adherent tissues such as ovarian tissue, peritoneum, intestine, and uterus, then proliferate to become endometrial lesions.<sup>4</sup>

The immune microenvironment of the women with endometriosis is found in many inflammations, angiogenesis, and endocrine signal. The molecular

profile shows the differences condition of immune response and inflammation gene expression between normal endometrium and endometriosis patients, proven by the existence of leukocyte signal dysregulation and cytokine receptor interaction on endometriosis.<sup>5</sup> The increasing level of activation macrophage, T cell, B cell is found on women with endometriosis, while the NK cell is decreased. Upregulation of Stem Cell Growth Factor b (SCGFB), IL-8, human growth factor dan *Monocyte Chemoattractant Protein 1* (MCP1) is found on endometriosis while IL-13 as an anti-inflammatory is decreased. Immune dysfunction and cytokine interactions stimulate the formation of endometriosis progression.<sup>6</sup> Overexpression of activation macrophage as a result of chronic inflammation in intrauterine and fallopian tube can eliminate the sperm and effects infertility.<sup>7</sup>

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In addition, unbalanced apoptosis signals and oxidative stress also promote the progression of endometriosis. Delbandi AA *et al* reported that BCL2 level as an antiapoptotic molecule in endometrium lesion is higher than normal endometrium. TGF-beta expression is increased in endometrium lesions, it can reduce the level of BAX protein. The dysfunction mechanism of an apoptotic signal can promote the growth of endometrium lesion.<sup>8</sup>

The etiology of endometriosis remains unclear. Sampson firstly recognized its theory of endometriosis at 1920 which called “retrograde menstruation” theory. Sampson was poured his thought that endometrial tissues has been transported by menstrual blood retrograde to the fallopian tube then peritoneal cavity. Those endometrial cells bind to the peritoneal mesothelial and take nutrition out from the blood, proliferate become endometrial implantation in the peritoneal.<sup>9</sup> Retrograde menstrual also promotes unbalanced ROS production through signaling pathway of Extracellular Signal-Regulated Kinase and Phosphatidylinositol 3 Kinase.<sup>10</sup>

This review article will more discuss the three main molecular mechanisms which are dysregulated and contributed to the progression of endometriosis. Considering that endometriosis development is related to the patient’s quality of life and infertility, these three main molecular mechanisms deserve further in-depth study. In addition, intensive research is expected to find molecular target for development of the diagnostic and therapeutic methods.

## MATERIALS AND METHODS

The narrative review was written initially by searching the recent publication in PubMed NCBI database and in the Google platform with the keyword “immune dysfunction on endometriosis”, “apoptosis dysregulation on endometriosis”, “oxidative stress on endometriosis”, “dysregulation of immune and endometriosis-associated infertility”, “ROS and endometriosis”. The references which has been taken also restricted from 2015 to 2021. There were 41 articles that correlated with dysfunction of immune, apoptosis, and oxidative stress on endometriosis were found.

## DISCUSSION

The progression of endometriosis may occur due to several signaling dysfunction in cellular and molecular mechanisms. Three signaling dysfunction during endometriosis progression which have been reported in several studies are; immune dysfunction, apoptosis signaling disturbance, and oxidative stress elevation.

### Mechanism of Immune Dysfunction on Endometriosis

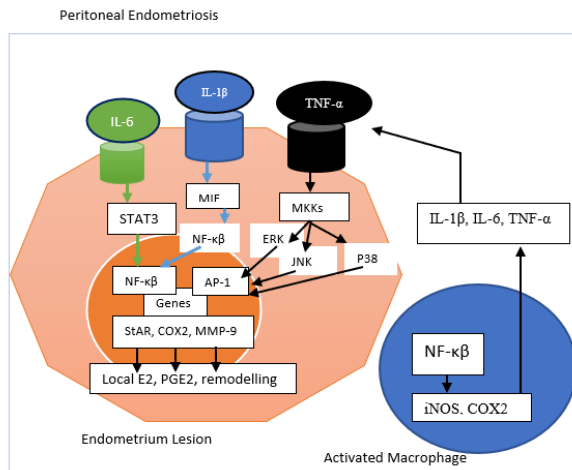
During menstrual, endometrium cells may migrate to the peritoneal area through retrograde menstrual. On the endometriosis lesion was found a number of activated macrophages, B cell, T cell, and low level of NK cell.<sup>4</sup> The abundance of activated macrophages in the microenvironment of endometrium lesion that grows in the peritoneal membrane facilitates the vein to attack to endometrium lesion. Thus, the endometrium lesion grows continually. Activated macrophage secretes

number of cytokines for modulating the normal cell function, but the macrophage dysregulation has occurred, and subsequently it causes neutrophil infiltration that implicated to activate the VEGF for neovascularization. Besides, the macrophage also decreases the IL-24, then proliferation and invasion of endometrium lesion are increased. It is supported with increased TGF-Beta in the microenvironment of endometrium lesion which stimulates macrophage activation on the surface of the Integrin alfa/beta.<sup>11</sup>

The macrophage will activate and converts to M2. It causes the stimulation of cytokine secretion, such as IL-10, IL-1, and IL-6 resulted in increasing of lesion growth and its proliferation. The occurrence of retrograde menstrual increases the polarization M2 then causes the increase of endometrium lesion proliferation through the STAT3 signaling pathway.<sup>12,4</sup> Reported that IDO-1 also has a role in the M2 polarization, endometrium lesion secretes IDO-1 that stimulates the polarization of M2.<sup>13</sup> Fractalkine that secreted from endometrium lesion also contributes to the M2 polarization and increases the MMP-9 expression. The decreasing of MMP-1 and MMP-2 also occurred. All events cause the increase of endometrium lesion invasion and endometriosis progression through MAPKs signaling.<sup>14</sup>

Besides macrophage cell dysregulation, T cell dysregulation has occurred. T cell secretes cytokines and T cell profile has been different compared with the normal endometrium. There are many CD8, CD4, and activated T cells in endometrium lesions. While the Th1 has decreased significantly, Th17 and IL-10 population have increased in the peritoneal fluid of endometriosis individual. It has been associated with the increasing of IL-27, IL-6, and TGF-Beta resulted in increasing the production of Th17 and IL-10. Consequently, increasing in the endometrium lesion invasion and proliferation is occurred.<sup>15</sup> IFN-Gamma, IL-10, IL-4, and IL-2 significantly increases in the microenvironment of endometrium lesion. Those cytokines stimulate the formation of the Th2 subset and inhibit the cytotoxic Th1. IL-4 is the Th2 cytokine that can increase the expression of mRNA 3 $\beta$ -hydroxysteroid dehydrogenase, which is the main enzyme for estrogen production. Therefore, this will increase the endometriosis progression through p38 MAPK, and p42/44 MAPK signaling pathway.<sup>16</sup>

The IL-6 was found abundant in endometrium lesion and its expression stimulated by IL-1 $\beta$  and TNF- $\alpha$ . The abundant IL-6 inhibit the differentiation of Th1 through the of the secretion of IFN- $\gamma$  and SOCS1 (*Suppressor of Cytokine Signaling-1*). Then, IL-6 promotes the differentiation of Th2 through the activation of the transcription factor, like nuclear factor p $\mu$  activated T cells or NFAT.<sup>17</sup> In addition to Th2, the naive T cell differentiates into a regulator T cells and suppresses the immune response for proliferating and activating the T cells, macrophage, dendritic cells, and natural killer cells. That immune suppression leads to the infiltration of T-reg on the endometrium lesion. It shows the poor prognosis. An increasing of T-reg of the T cell population in the peritoneal fluid induces the decrease of immune response and inhibits in recognizing and eliminating the endometrium lesion. Consequently, the endometrium lesion will persist, grow and survive.<sup>18</sup>

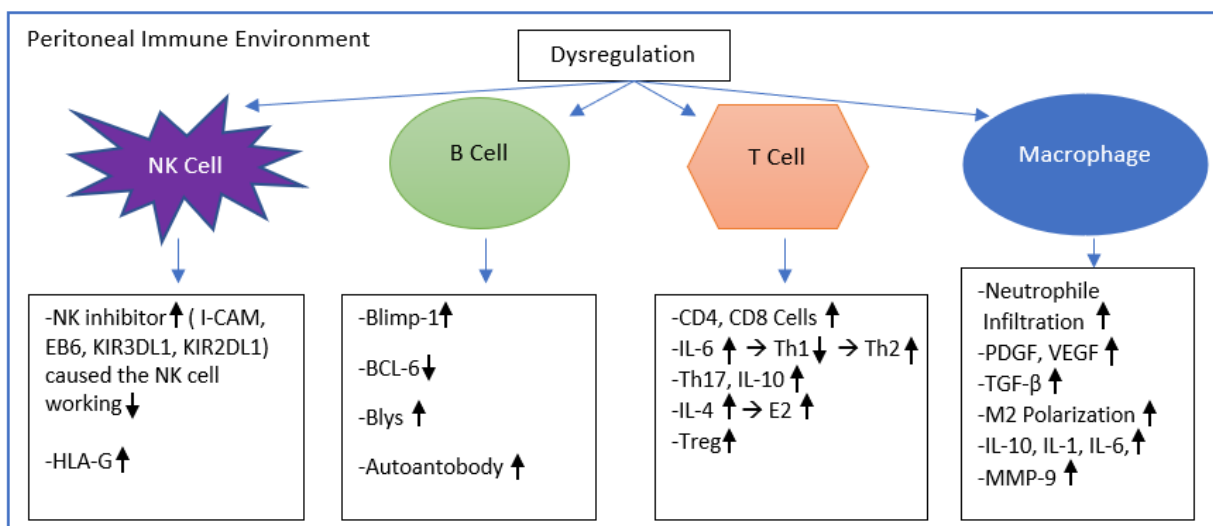


**Figure 1.** The cytokines interaction induce progression of endometrium lesion. The production of iNOS and COX2 by NF- $\kappa$ B through the activated macrophage. It secretes the cytokines like IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . Those cytokines bind to their receptors on the endometrium lesion and activated the pathways of STAT3, NF- $\kappa$ B, MKKs then activated the transcription factor of NF $\kappa$ B and AP-1 and stimulate the production of local E2, PGE2 and MMP-9 for remodeling and adhesion cell to increase the progression of lesion.

The activated macrophage in the peritoneal has secreted the Nitric Oxide Synthase and COX2 through interferon regulatory factors, NF- $\kappa$ B and *nuclear factor-2*. Its activation has facilitated by STAT, p38, ERK, and JNK signaling pathways. Besides, the activated macrophage also has secreted many cytokines, like IL-1, IL-6, IL-8, IL-10, IL13, TNF- $\alpha$ , growth factor, VEGF, and platelet-derived growth factor or PDGF. TNF- $\alpha$ , IL-1 $\beta$ , dan IL-6 bind their receptor in the membrane surface of the endometrium lesion. Those cytokine receptors activate PI3K, MKK, JNK, p38, and IKK

pathways for inducing inflammation response and invading the mediators like StAR, COX2, and MMP-9. Through the activation of NF- $\kappa$ B, and AP1, the forming of estradiol local, PEG2, NCOA-1 isoform, and tissue remodeling has occurred. Those formations will increase the endometrium lesion growth (Figure 1). An interaction complex of estradiol/ESR2/NCOA-1 increases the IL-1 $\beta$  for inducing monocyte differentiation became the macrophage. Therefore, the cytokine interactions in the endometrium lesion and the macrophage role can lead to the initiation, survival, and progression of endometriosis.<sup>4</sup>

The granules of NK cells contained the granzyme, perforin, and IFN-gamma which induced of the lesion apoptosis.<sup>4</sup> But, the NK cell dysregulation has occurred. Some cytokines that can inhibit the NK cells activity have been found in high concentration in the peritoneal fluid of endometriosis as well as the HLA-G and the HLA-E. High concentration of *Immunoreceptor Tyrosine-based Inhibitory Motif Killer Cell Inhibitory Receptors* (ITIM-KIRs) which contain the Immunoglobulin domain such as KIR2DL1, KIR3DL1, EB6, and I-CAM also found in the peritoneal fluid of endometriosis. Those have a role to suppress the NK cytotoxic cell activations. A high level of HLA-G facilitates interacting with immune cells and binding to NK cells. It causes the retrograde menstrual tissues transform and became the lesion.<sup>19</sup> In addition to T cells, NK cells, macrophage, T-Reg cells, B cells are also dysregulated. Although the T cells were suppressed, the populations of B cells significantly increased, and the B lymphocyte inducer of maturation program or Blimp-1 has been found higher than normal endometrium.<sup>20</sup> The B lymphocyte stimulator or Blys that the role is very important for facilitating the differentiation of the B cells into plasma resulted in antibody. The increased hyperactivity of the B



**Figure 2.** The Summary of Immune Cells Dysregulation in Endometriosis

Neutrophile infiltration occurred, and macrophage dysregulation could secrete an abundance of cytokines; it stimulates PDGF and VEGF increased for neovascularization, increased TGF- $\beta$  and M2 polarization induces increased cytokines and MMP-9 for increasing the endometrium lesion invasion. T cell profile in the endometrium lesion found increased CD4 and CD8 and induces the increased IL-6, decreased Th1, and increased Th2, it cause attenuated cytotoxicity response, increased Th17, IL-10, IL-4, and T-reg make the lesion to proliferate and attenuate the immune response. Dysregulation of B cell induces the increase of Blimp-1, Blys, and autoantibody and decreased BCL-6; this dysregulation allow the lesion to survive. NK cell dysregulation also occurred; increased I-CAM, EB6, KIR3DL1, KIR2DL1, and HLA-G inhibit the NK cell cytotoxic responses and allow the lesion to grow.

lymphocyte can contribute to the endometriosis progression through the autoantibody which can break the endometrium, but other studies explain the role of hyperactivity of the B lymphocyte in endometriosis is still unclear.<sup>21</sup> Several dysregulations in the immune cells of endometriosis have been summarized in the figure 2.

Endometriosis is a multifactorial disease, many factors can increase the formation of endometriosis; several gene mutations, epigenetic and environmental factors interact to form endometriosis.<sup>22</sup> Several genes involved in immune dysfunction correlated with chronic inflammation.<sup>23</sup> Immune dysregulation can also increase due to the presence of DNA methylation and mRNA expression that regulate inflammation.<sup>22</sup> Increased mRNA expression of the TRPA1 gene and hypomethylation are found in endometriosis. TRPA1 encodes an ion channel protein that regulates pain through neuronal activity.<sup>24</sup> Hypomethylation of the SF-1 gene which plays a role in the regulation of steroid hormone and aromatase biosynthesis is also found in peritoneal and ovarian endometriosis.<sup>25</sup> Increased steroid hormones can cause increased inflammatory cytokine secretion and changes in immune cell activity resulting in immune dysregulation.<sup>26</sup> This is also in line with the increased expression of beta receptor mRNA in endometriosis. Increased beta estrogen receptors can induce COX-2.<sup>27</sup>

Progesterone resistance is also associated with increased inflammation in endometriosis.<sup>26</sup> Hypermethylation of the progesterone receptor A (PGR-A) can lead to decreased PGR-A mRNA expression and is associated with progesterone resistance.<sup>28</sup> Hypermethylation of the progesterone receptor B (PR-B) is associated with progesterone resistance in lesions. Endometriosis so that it has the potential to be a biomarker for the diagnosis of endometriosis.<sup>29</sup> Inflammatory mediators can interact with sensory neurons and induce pain signals. PGE2, IL-6, and IL-1 $\beta$  are inflammatory mediators that can induce pain in endometriosis.<sup>30</sup> Increased expression of P2X3 receptor coding genes through the ERK/MAPK activation cascade is also associated with pain in endometriosis lesions.<sup>31</sup> Furthermore, cytokines such as IL-10 and IFN which increase due to the dysregulation of cytotoxic T cells can increase MMP-2 expression.<sup>32</sup> Increased MMP-2 is associated with DNA methylation on MMP-2 and induces increased invasion of endometriosis lesions.<sup>33</sup> Therefore, immune system dysregulation in endometriosis involves immune cell dysregulation and hormonal factor. Furthermore, immune system dysfunction in endometriosis is related to epigenetic factors through inflammation. This factor leading increased the development of endometriosis. Therefore, it can be assumed that immune system dysfunction in endometriosis is the main molecular mechanism factor for the formation of endometrial lesions.

### **Mechanism of The Signal Apoptosis Dysregulation on Endometriosis**

Apoptosis failure for retrograde menstrual tissues and abnormal apoptosis for immune cells are associated with the endometriosis progression.<sup>14</sup> By understanding the molecular mechanism related to the apoptosis

dysregulation on the endometriosis tissues and immune cells, then easy to determine the molecular etiology for new therapy agent development. It has been reported that the reduction of apoptosis in the endometriosis ectopic tissues is occurred. It has supported by finding of anti-apoptotic BCL-2 protein in high concentration in endometriosis lesion. The increase of BCL-2 protein accords with the increased of the c-Myc protein which regulate the cell cycle and the increase of TGF- $\beta$ . While the apoptosis molecule such as BAX has decreased. The apoptosis dysregulation that happened in the endometrium lesion has associated with the retrograde menstrual tissues ability to escape from the immune surveillance lead to increasing of the endometrium lesion growth and proliferation.<sup>34</sup>

Apoptosis signal can be occur in two ways, they are the intrinsic and the extrinsic pathway. The intrinsic pathway runs via mitochondria and the extrinsic pathway carry out via death receptor-mediated mechanism. The dysregulation of intrinsic pathway by suppression its molecular pathway. It is proven by the expression of p53 in the endometrium, the expression of BCL2 protein in the peritoneal are found high.<sup>35,36</sup> Whereas the dysregulation of the extrinsic pathway occurs in the Fas receptor and its ligan. Fas receptor proteins (DR2/CD95/Apo-1) are the protein of membrane type-1 (mFas) that can bind the extracellular domain of FasL (CD95L/CD178/Apo-1L). mFas also binds the cytoplasmic domain which transducing the death signal. The death signal has been mediated by the interaction of Fas/FasL. The death signal has an important role in maintaining the immune surveillance.<sup>36</sup>

FasL has been expressed in the normal endometrium cells and its expression has been stimulated by cytokines released from the macrophage, like PDGF and TGF- $\beta$ 1. The increase of IL-8 in the peritoneal fluid of endometriosis individuals would cause the increasing of the FasL expression in the endometrium cells. Although the FasL expression has increased, it has not induced apoptosis in the endometriosis stromal cells. It has been caused by the decrease of the Fas receptor expression. The ectopic epithelial cells in the endometriosis stimulate an increase in FasL expression and lead to low the Fas receptor expression. The decrease of Fas receptor expression also caused by the apoptosis of cytotoxic T cells which expressed the Fas receptor.<sup>37</sup> Accordingly, the apoptosis dysregulation would cause the endometriosis epithelial cells to avoid the immune surveillance. It can induce the growth of the endometrium lesions.

Apoptosis dysregulation can occurs in TNF- $\alpha$ . Its population was increased by retrograde menstruation. TNF- $\alpha$  binds the TNF Receptor or TNFR for inducing of caspase-8 and caspase-9 expression then mediating the apoptosis of retrograde menstruation tissues. On the endometriosis individual, the number isoform of Nuclear Receptor Coactivator or ESR2 would bind the Apoptosis Signal Regulating Kinase 1 or ASK 1, caspase-8 and caspase-9 then suppress the extrinsic apoptosis signaling in the retrograde menstrual tissues. The increasing of PGE2 on endometriosis would like to increase the ratio of BCL/BAX protein in the mitochondria, accordingly the intrinsic apoptosis signaling has been suppressed. On the endometrium lesion, reported that the level of FasL

has increased then could bind its receptor or Fas receptor in the cytotoxic T cell membranes. Thus, the cytotoxic T cell has died. This has represented the main defense mechanism of endometrium lesion to avoid the cytotoxic T cells during the retrograde menstrual occurred.<sup>4</sup>

The dysregulation of the apoptosis signal also occurred through the NF- $\kappa$ B and Akt pathways. Normal endometrium has shown that NF- $\kappa$ B and Akt pathways have been inactivated. It made the stimulation of the Bad/Bax protein dephosphorylation. The Bad/Bax disassociated from 14-3-3 protein has caused the translocation of the Bas/Bax protein from the cytosol to the mitochondria. Then, the interaction between Bad/Bax protein with the Bcl-2/Bcl-XL protein has occurred. That interaction has implicated for the mitochondria to secrete the c-cytochrome into the cytosol and activate the caspase-3 and the enzyme which accelerated the apoptosis of endometrium cells. While endometriosis has shown that NF- $\kappa$ B and Akt pathway has activated and stimulated the cells stand to survive. Its activation has controlled the Bad/Bax protein phosphorylation. The Bad/Bax binding into 14-3-3 protein has caused the Bad/Bax would survive to release into the cytosol and the interaction between the Bad/Bax and Bcl-2/Bcl-XL has not occurred. Thus, endometrium cells would not has apoptosis.<sup>8</sup>

### Mechanism of The Oxidative Stress Dysregulation on Endometriosis

In the normal condition, the homeostasis of ROS and antioxidant has been maintained. An excessive ROS level has induced the oxidative stress, endometriosis, and has implicated to the women's reproductive quality.<sup>38,39</sup> The oxidative stress has broken the lipid, protein, and DNA. The number of ROS production has damaged the cellular function through the NF- $\kappa$ B transcription factor activation. Its activation has stimulated the expression of many genes related to the initiation process and the endometriosis progression. The erythrocytes, the tissue apoptosis products of endometriosis, the debris cells that were released in retrograde menstrual tissues have migrated to the peritoneum cavity. That migration has been induced by the macrophages which became the main inducer in oxidative stress in the peritoneum cavity. Moreover, excessive iron in the peritoneal fluids of endometriosis individuals can be the cause of the ROS activation by Fenton reaction. The formation of ROS in the peritoneal microenvironment can increase the invasion and the growth of retrograde menstrual tissues.<sup>38</sup>

The number iron would expand the endometrium lesion in the animal model by stimulating the endometrium epithelial cell proliferation. Besides, the number iron would increase the NO production, thus induce the macrophage to fail to phagocytose the endometrium lesion. An excessive iron that cause the formation of oxidative stress is due to the dysregulation of ROS detoxification signaling. Retrograde menstrual which has stimulated by the oxidative stress hyperactivation would activate the ERK, PI3K/AKT/mTOR signaling pathways. That activated signaling pathways would stimulate the adhesion formation, angiogenesis, and endometrium lesion proliferation.<sup>10</sup>

The presence of the iron-rich erythrocytes, the endometrium apoptosis tissues, and the debris cells in the pelvic cavity has stimulated the ROS formation in the mitochondria. ROS hyperactivity then stimulates the increase of the macrophage level in secreting the cytokines like TNF- $\alpha$  and IL-6. Those cytokines could activate the ERK, and PI3K/AKT/mTOR signaling pathways by binding into the receptor in the endometrium lesion membrane, like TNFR, and IL-6 receptor. That signaling pathway is the way for cell adhesions, angiogenesis, and proliferation of endometrium lesion. ROS production which has excessive also could cause cell function failure. It has happened by the alteration of the gene expression profile through the NF- $\kappa$ B activation and made the upregulation signaling cascade for increasing the inflammation cytokine secretion in the endometrium lesion. As a result, the endometriosis progression has increased.<sup>4</sup>

The oxidative stress in the endometrium lesion microenvironment could cause the activation of p38 MAPK and stimulate the early aging of the fetal tissues. Furthermore, oxidative stress activates the ERK signaling and increases the endometriosis progression. Embryonic stress also can be occurred in endometriosis which stimulated by oxidative stress. The embryonic stress has characterized by the increase of TNF- $\alpha$  and IL-1 $\beta$  that in a high level. High cytokine levels could activate the NF- $\kappa$ B then the placenta apoptosis can occur. The Forkhead Box O3a or FOXO3a also has activated the NF- $\kappa$ B pathway through the IKK phosphorylation for degrading the Inhibitor Kappa $\beta$  or I $\kappa$ B then the NF- $\kappa$ B transcription factor could translocate into the nucleus and activate the gene expression that related to the inflammation and the apoptosis response. Besides through the directly IKK phosphorylation, FOXO3 also could activate BCL10 for degrading the IKK, then NF- $\kappa$ B activated.<sup>40,41</sup>

The body has maintained the homeostasis of the oxidant and an anti-oxidant level during pregnancy. TNF- $\alpha$  during that time has increased and the progesterone level alteration has occurred. First, TNF- $\alpha$  has activated the cell signaling pathway complex through the second messenger or cAMP like Keap1-Nrf2, NF- $\kappa$ B, and MAPK signaling pathways. Then increased the cytokine level and the genes expression alterations related to the antioxidant. When the FOXO3 has increased, that condition could stimulate the binding of Keap1-nrf2 and cause the antioxidant level to decrease. Then, I $\kappa$ B has stimulated the NF- $\kappa$ B released. It could cause apoptosis and cytokine levels to increase. Accordingly, the alteration mechanism of the FOXO family has occurred in increasing oxidative stress, although it has also a role in the reproductive system effects. Another pathway that has included in oxidative stress into apoptosis by FOXO is the JNK pathway. It could make the FOXO dephosphorylation through the cAMP then induced the FOXO1 to translocate into the nucleus and stimulated the apoptosis.<sup>41</sup> Based on the mechanism of oxidative stress dysregulation in endometriosis, several molecules are involved such as TNF- $\alpha$ , NF- $\kappa$ B, and IL-6 which can trigger inflammation. NF- $\kappa$ B activation is also involved in the dysregulation of apoptotic signals that prevent endometriotic cell apoptosis. So that it can be strongly suspected that

immune system dysregulation, apoptotic signal and oxidative stress dysregulation are correlated each others, which can be spearheaded by inflammation occurs in immune system dysfunction.

## CONCLUSION

The signaling dysregulation that occurs in endometriosis has a role in the development of endometriosis. Three main mechanisms have been reported for dysregulation during the development of endometriosis. Namely immune system signaling dysfunction, apoptotic dysfunction, and dysregulation of oxidative stress signaling. Retrograde menstruation has been a long-held theory in pathogenesis of endometriosis. Retrograde menstrual tissue migrates into the pelvic cavity and outside of the pelvis leading to endometriotic lesions. Thus, three mechanisms have been supported and compatible with the theory of retrograde menstruation.

Some immune cells such as macrophages have increased in the peritoneal fluids then stimulate the secretion of proinflammatory cytokines (IL-6, IL-8), and angiogenesis factors (PDGF, VEGF). NK cells in endometriosis have suppressed cytotoxic T cells so that the lesion has not cleared up. Th2 cells have differentiated into T-reg cells to suppress activation of T cells, macrophages, and B cells in endometriosis. In addition, hormonal and epigenetic factors also induce immune dysregulation through inflammation. Dysregulation of apoptotic signaling has occurred in both the intrinsic and extrinsic pathways which can then stimulate the survival of endometriosis lesion to proliferate. NCOA-1/ESR2 can bind the ASK1, caspase-8, and caspase-9 then suppress the intrinsic apoptotic pathway, whereas activated Akt and NF- $\kappa$ B can inhibit the intrinsic apoptotic pathway.

Dysregulation of oxidative stress signaling has occurred in endometriosis due to an imbalance in ROS production. Furthermore, this imbalance condition has suppressed macrophage cells to phagocytize endometrial lesions from retrograde menstrual tissue through activation of the ERK pathway, PI3K/AKT/mTOR leading to the development of endometriosis.

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