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The Molecular Basis of Adenomyosis Development

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Abstract

Adenomyosis is a benign gynecological disease frequently affecting women of reproductive age. It has a negative impact on the quality of life, causing bleeding disorders, dysmenorrhea, chronic pelvic pain, and infertility. However, the molecular mechanisms involved in adenomyosis development remain unclear. This paper summarizes the reports found in the MEDLINE database on the molecular mechanisms involved in the development and progression of uterine adenomyosis. The literature search included the following terms: "adenomyosis," "adenomyoma," "pathogenesis," "molecular mechanisms," and "gynecological disorders." Only peer-reviewed, English-language journal articles were included. This review focuses on the molecular genetics, epigenetic modifications, and pivotal signaling pathways associated with adenomyosis development and progression, which will provide insights into and a better understanding of its underlying pathophysiology.

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INTRODUCTION

A large number of women are affected by adenomyosis, which can adversely affect quality of life. Based on diagnostic criteria, the prevalence of the adenomyosis has been reported to range from 5% to 70% (Taran et al., 2013). Despite the high prevalence rates, the key molecular mechanisms underlying the disease have been poorly understood. Common symptoms of adenomyosis include dysmenorrhea, menorrhagia, and pelvic pain (Peric & Fraser, 2006; Sammour et al., 2002), which interfere with the normal function of the uterus, including fertility and implantation (Garavaglia et al., 2015; Yazbeck et al., 2015). Therefore, it is important to identify the molecular mechanisms involved in the pathogenesis of adenomyosis for better prevention, treatment, and diagnosis of this condition. Many researchers have attempted to understand the molecular mechanisms underlying adenomyosis and to develop new therapies. This paper briefly reviews the potential molecular mechanisms that may provide insight into the pathophysiology and development of adenomyosis.

General Aspects of Adenomyosis

Adenomyosis is a benign uterine condition characterized by the presence of heterotopic epithelial cells, endometrial glands, and

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stroma within the myometrium, which causes thickening or swelling of the uterus (Harada et al., 2016; Jain & Goel, 2012). Adenomyosis development is associated with a hormonal imbalance. Common adenomyosis symptoms and signs include dysmenorrhea, chronic pelvic pain, and dyspareunia (Proctor & Farquhar, 2006). Moreover, adenomyosis may cause infertility or subfertility (Harada, et al., 2016). Several studies have shown that adenomyosis is associated with both hormonal and autoimmune factors (Garavaglia et al., 2015O; ta et al., 1998), but the pathophysiology of adenomyosis is still largely unknown. Currently, adenomyosis is commonly diagnosed by endometrial biopsy, magnetic resonance imaging, and transvaginal ultrasonography (Dueholm, 2006; Tamai et al., 2005; Wortman, 2008). However, these diagnostic methods have some limitations such as the limited field of view, low specificity, and difficulty in detecting early-stage disease (Bazot et al., 2002; Reinhold et al., 1998; Tamai et al., 2005). Therefore, more precise studies evaluating the molecular mechanisms involved in adenomyosis are required to design suitable clinical trials and allow prevention, pappropriate treatment, and prompt diagnosis.

Molecular Events in Adenomyosis Development

1. Genetic mutations

It has been suggested that genetic mutations in endometrial cells also induce adenomyosis. However, to date, the role of genetic mutations in adenomyosis has not been fully documented. Only a limited number of experimental studies confirming the mutational status of genes have been conducted to date. One study reported that mutations of estrogen receptor alpha (ERα) gene (ESR1) were found in adenomyosis (Oehler et al., 2004). The ERα has been mapped to chromosome 6q25.1 and is encoded by the ESR1 gene. ERα is a ligand-dependent transcription factor whose expression is commonly regulated by estrogen and is functionally implicated in cell growth and integrity (Chen et al., 2014). In the uterus, ERα protein has been known to contribute to fertility, mammary gland maturation, and induction of ovulation (Lee et al., 2012). Another report indicated that DNA-binding domain mutations of ESR1 can lead to defective transcriptional activation. In adenomyosis, the presence of two point mutations (P129R, M427I/L429M) in ESR1 has been confirmed (Oehler et al., 2004). Although the above study identified only a 5% prevalence of ESR1 mutations, this finding implies that the mutations may induce development of adenomyosis.

2. Changes in cellular phenotype

Epithelial to mesenchymal transition (EMT) refers to the phenotypic transition of epithelial cells to mesenchymal cells, which ultimately results in the conversion of epithelial cells into cells with metastatic and invasive potential (Son & Moon, 2010). Although the transition of these cells is essential during development (Kalluri & Weinberg, 2009), it is also considered an undesirable phenomenon in relation to progression in various diseases. Reprogramming of cells by EMT mechanisms is closely linked to changes in different regulatory networks. The dysregulation of epithelial cells is caused by changes in various regulatory steps, including transcription and translation. One of the major molecular changes occurring during EMT is a reduction in CDH1 expression (Kalluri & Weinberg, 2009). Also, several reports have indicated that transcription factors such as Snail, Slug, and Twist can induce EMT in cancer (de Herreros et al., 2010; Lamouille et al., 2014; Y. Wang et al., 2013). Determining the relationship between EMT control mechanisms and various signaling systems will help in better understanding of adenomyosis development

2.1. Wnt/β-catenin signaling

Several reports have described Wnt/β-catenin signaling to play an important role in EMT progression (Y. G. Jiang et al., 2007; Shan et al., 2015). β-catenin is a key factor in the canonical Wnt signaling pathway. Several reports have indicated that stabilization of β-catenin expression is associated with many different cancers, including ovarian, colon, and endometrial cancer. Cancer pathogenesis likely involves the abnormal accumulation of β-catenin in the nucleus (Polakis, 2000). In general, in the absence of Wnt signaling, cytoplasmic β-catenin is degraded through phosphorylation by a β-catenin destruction complex, including kinases glycogen synthase kinase-3 beta (GSK3β), adenomatous polyposis coli (APC), and casein kinase-1 (CKI).

However, in the presence of Wnt signaling, GSK3β, APC, and CKI bind to the Low-density lipoprotein receptor-related proteins 5 and 6 (LRP5/6) receptor, which leads to inhibition of GSK3β-, APC-, and CKI-mediated β-catenin phosphorylation. Therefore, stabilization of β-catenin leads to translocation of the protein into the nucleus, which activates Wnt signaling and target genes involved in cell proliferation, such as c-MYC and cyclin D1 (He et al., 1998; Shtutman et al., 1999). One study revealed that the stabilization of β-catenin leads to the activation of mesenchymal cell markers such as ZEB1 and SNAIL in endometrial epithelial cells. In addition, Cadherin-1 (CDH1) protein expression has been shown to be reduced in endometrial epithelial cells (Oh et al., 2013). These results suggest that a dominant stabilized β-catenin expression may play an important role in the pathogenesis of adenomyosis.

2.2. Notch signaling

Notch signaling also contributes to adenomyosis development by EMT progression (Qi et al., 2015). It is well known that notch signaling regulates the growth of cells and developmental processes of various organs (Lai, 2004). The Notch receptor is a membrane protein that includes Notch1, Notch2, Notch3, and Notch4. Delta-like and Jagged are the most well-known ligands of the Notch receptor. Theses ligands commonly have a Delta/Serrate/LAG-2 (DSL) domain that can bind to the Notch receptor. Upon ligand binding, the Notch intracellular domain (NICD) is cleaved by several factors such as protease and gamma-secretase enzymes, which results in its release into the nucleus to regulate gene transcription (Yamamoto et al., 2014). It has been reported that genes associated with EMT induction are also regulated by Notch signaling (Z. Wang et al., 2010). One study showed that Notch1 levels in adenomyosis are higher than those found in the normal endometrium. In addition, expression of Numb, a negative regulator of Notch signaling, is reduced, while the expression of mesenchymal cell markers such as N-cadherin, Slug, and Snail is also increased (Qi et al., 2015). These data indicated that the Notch signaling pathway may contribute to the development and pathogenesis of adenomyosis.

2.3. TGF-β signaling

Another important pathway that causes adenomyosis development is the transforming growth factor beta (TGF-β) signaling pathway (Shen et al., 2016; Yen et al., 2017). TGF-β is a member of the TGF superfamily that plays an important role in cell regulation of apoptosis, blocking of the cell cycle, and differentiation (D. T. Wu et al., 2005). Thus, TGF-β signaling is closely associated with cell homeostasis and various human diseases. TGF-β activates the TGF-β receptor II through the formation of a heteromeric complex, leading to the TGF-β receptor II-induced phosphorylation of TGF-β receptor I. Subsequently, activated TGF-β receptor I phosphorylates the C-terminal of serine residues of the Receptor activated-Smad (R-SMAD) transcription factors. Thus, phosphorylated R-SMADs can translocate into the nucleus after complex formation with Smad4. Here, the Smad complex induces the expression of target genes through interaction with co-activators such as CREB binding protein (CBP)/p300 (Verrecchia & Mauviel, 2002; Zi et al., 2012). Some reports have indicated that TGF-β signaling induces expression of Snail, Zeb1 and HMGA2 proteins, which are known to induce factors involved in EMT (Miyazono, 2009; Xu et al., 2009). Results from microarray-based gene expression studies have determined that TGF-β is strongly expressed in adenomyosis-induced mouse models (Shen et al., 2016). These results suggest that the TGF-β signaling pathway may be an important target in the study of adenomyosis development.

3. Epigenetic changes.

Aberrant epigenetic events have been thought to be involved in the development of diverse diseases. Epigenetic changes involving methylation of DNA, histone modifications, and non-coding RNA have been identified in many cancers such as breast, prostate, ovarian, and endometrial cancer (Balch et al., 2009; Stampoliou et al., 2016; Y. Wu et al., 2015). Thus, a better understanding of epigenetic changes in cancer tissues may contribute to the development of useful biomarkers and prevention of gynecological diseases.

Epigenetic changes in DNA expression have been studied in the development of adenomyosis. Histone modification is a

phenomenon that can alter gene function without altering DNA sequences. To form the nucleosome, DNA wraps around special proteins called histones. The overall structure of the nucleosome can be modified by different modifications including acetylation, phosphorylation, ubiquitination, and methylation of histone proteins. These modifications alter the accessibility of transcription factors to the target DNA sequences (Marino-Ramirez et al., 2005). It has been suggested that an aberrant histone modification may contribute to adenomyosis progression. Class I histone deacetylases (HDACs) have been shown to be involved in the development of adenomyosis. HDACs remove the acetyl groups from histone proteins, which results in the promotion of gene transcription (Seto & Yoshida, 2014). In adenomyosis, the expression of both HDAC1 and HDAC3 isoforms is higher in the eutopic and ectopic endometrium than in the normal endometrium (Liu et al., 2012). It has also been reported that DNA methyltransferase (DNMT) proteins involved in DNA methylation may be implicated in adenomyosis development. Levels of DNMT1 and DNMT3B isoforms were found to be higher in the ectopic endometrium than in the normal endometrium, whereas DNMT3A levels were lower in the eutopic and ectopic endometrium (Liu & Guo, 2012). Another study reported that aberrant expression of long non-coding RNA (lncRNA) also contributes to the development of adenomyosis, which was a new finding. The lncRNA is known to play an important role in gene regulation such as transcription and translation (Cao, 2014). One study reported a total of 165 lncRNAs were abnormally expressed in the eutopic endometrium with adenomyosis; whereas, no abnormal lncRNA expression was found in endometrium without adenomyosis (J. F. Jiang et al., 2016). Similarly, a study evaluating lncRNA expression patterns showed that 576 lncRNAs were abnormally expressed in the ectopic endometrium with adenomyosis (Zhou et al., 2016). Therefore, these results suggest that abnormal epigenetic modifications may be critical factors in adenomyosis development. Evaluation of these epigenetic changes may be helpful in defining treatment, prevention, and diagnosis of adenomyosis.

CONCLUSIONS

Gynecological diseases have recently been attracting much attention with the objective of improving the quality of life of women with these conditions. Thus, there has been a great increase in the number of molecular studies investigating the causes of gynecological diseases. Although many studies on adenomyosis have been performed, the understanding of the underlying molecular mechanisms is inadequate as the altered molecular pathways in adenomyosis are very complex and have shown different specificities in different cell types. Understanding the underlying molecular mechanisms is crucial for the development of clinical trials and for the treatment, prevention, and diagnosis of gynecological diseases involving adenomyosis. Thus, we hope that more advanced research results will accumulate in the future.

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