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Review

Fetal programming theory: Implication for the understanding of endometriosis

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ABSTRACT

Comparison of the transcriptomes and proteomes of the decidualization-specific genes that express high vs low levels of the eutopic and ectopic endometrium of women with endometriosis compared with controls, could be useful in understanding the pathogenesis of endometriosis. Genome-wide comparison between decidual tissue and non-decidual tissue identified many genes significantly modulated in the process of decidualization. Comparison of eutopic endometrium and endometriotic sites also revealed up- and down-regulated genes. A combined analysis of the experimental data showed specific genes up-regulated both at the endometriotic site and in the decidualization process, representing a broad diversity of molecular functions, including cell cycle regulation, angiogenesis and adhesion molecules. In contrast, down-regulated genes identified in endometriosis among genes overexpressed in decidualization encode Müllerian embryogenesis, which includes transcription factors, hormonal regulation and cytokine expression. The mechanism responsible for insufficient decidualization in endometriosis may be mediated through down-regulation of the Müllerian embryogenesis-related genes. In conclusion, a range of decidualization resistance has been associated with endometriosis. Future study will identify the putative mechanisms relating epigenetic changes of decidualization susceptibility genes in early life to the risk of developing endometriosis in adulthood.

Contents

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1. Introduction

Despite a great advancement in identifying disease- and host-susceptibility genes using genome-wide or (epi)genetic studies, the majority of endometriosis cases are still underrepresented. The challenge in post-genetic studies era is to investigate functional causative genetic and environmental epigenetic factors of endometriosis.

Uterine endometrium undergoes structural and functional changes essential for uterine receptivity during the menstrual cycle in fertile women [1]. Endometrial cells establish their dynamic gene expression signature programs to endow them with the requisite set of cellular functions by phase-dependent expression throughout the menstrual cycle [2]. The menstrual cycle-specific proteins, which are influenced by steroid hormones, act by regulating gene expression through DNA methylation, histone acetylation, chromatin remodeling and the action of small-interfering RNAs and microRNAs [1]. The most highly expressed gene signature in the proliferative phase is characterized by angiogenesis, inflammation and immune function [2]. Comparison of differentially regulated genes in the window of implantation occurring during the mid-secretory phase revealed regulation of host defense mechanism, immune function and tissue remodeling [3].

The decidualization process is characterized by stromal cell proliferation and differentiation into decidual cells. Progesterone-regulated genes are necessary for adequate decidualization process and successful implantation [1]. Decidual cells promote expression of differentiation marker proteins such as insulin-like growth factor (IGFBP) 1, prolactin (PRL), glycodelin (also known as progesterone-associated endometrial protein, PAEP), leukemia inhibitory factor (LIF), interleukin-1 receptor (IL1R), homeobox A10 (HOXA10), Forkhead Box O1 (FOXO1), CCAAT/Enhancer Binding Protein-beta (C/EBPbeta) and glycogen synthesis, indicative of decidualization [4,5]. Gene expression is regulated by the acetylation-deacetylation switch, which depends on the menstrual cycle through the action of histone acetyltransferases (HATs) and histone deacetyltransferases (HDACs) [1]. These decidualization-specific genes might be under genetic and epigenetic controls. Therefore, abnormal phenotypes in decidualization can be due to changes in (epi)genetic modifications at specific loci, which may be associated with endometrial pathologies, including implantation failure, pregnancy loss, preeclampsia and endometriosis [1].

We searched aberrantly expressed genes in endometriosis among target genes that are up-regulated during the process of decidualization and normal window of implantation.

2. Review of the literature

A review of the literature was conducted to investigate current state of gene expression studies of decidualization and endometriosis. The techniques now available include microarray-based genome-wide gene expression profiling, high-throughput genome-wide technology, genome-wide association studies, exon microarray analysis, transcriptome RNA sequencing, DNA methylation profile, copy number variations, and their data set analyses. In a typical genome-wide data analysis, significantly differentially expressed genes are determined between disease samples and their normal counterpart. A Medline search of the literature was performed using the key words endometriosis, genome wide, gene expression profiling, pathway analysis, susceptibility gene and decidualization. English-language publications in PubMed and references from relevant articles published up to July 2013 were analyzed. References in the studies identified were also searched.

3. Results

3.1. Specific role of genes associated with the decidualization process

Decidualization includes morphological and biochemical changes of the fibroblast-like stromal cells by the action of ovarian steroids 17β-estradiol and progesterone [6]. We first compared the endometrial gene expression profile of decidualization to that of non-decidualization. Genome-wide expression profiling and proteomics studies identified a plethora of target genes and proteins with potential roles in decidualization and implantation [2–4,6–22]. Here, we analyzed 20 published datasets that are up- and down-regulated during the process of decidualization and normal window of implantation to increase the power of the identification of differentially expressed genes. Although the mechanisms regulating the regional decidual cell differentiation are complex, genome-scale approaches revealed that a number of specific genes are implicated in the decidualization process during pre-implantation. 107 Genes involved in the steroid-regulated pathways (estrogen receptor (ER), progesterone receptor (PR) and FK506 binding protein 4 (FKBP4)), transcription factors (HOXA10, FOXO1 and C/EBPbeta), cell-cycle molecules (cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors), hormone (prolactin (PRL)), cytokines (interleukin-11 (IL11), leukemia inhibitory factor (LIF) and transforming growth factor (TGF)-beta), signalings (Indian hedgehog (IHH), chicken ovalbumin upstream promoter transcription factor 2 (COUP-TF2), bone morphogenic protein 2 (BMP2) and Wnt/beta-catenin), growth factors (insulin-like growth factor (IGF), IGF-binding protein (IGFBP), hepatocyte growth factor (HGF) and heparin-binding epidermal growth factor (HBEGF)), angiogenesis (vascular endothelial growth factor (VEGF), angiopoietins (ANGPTs) and Tie2), metabolism (prostaglandins and cyclooxygenase 2 (COX2)) and adhesion (integrin and trophinin (TRO)), were up-regulated [2–4,6–22]. A number of genes have the potential roles of embryonic and uterine factors in implantation process, but only a small number of them, including IGF, IGFBP, PRL, HOXA10, FOXO1, C/EBPbeta, IL11 and LIF, are critical to this process. This study provides valuable information for understanding the potential roles of uterine genes in the progression of decidualization.

Table 1 and Supplementary data show selected functional category lists of up- and down-regulated genes identified in endometriosis among genes overexpressed in decidualization.

3.2. Endometriosis susceptibility genes

Secondly, we investigated whether endometriotic cells and decidual cells share any distinctive functional characteristics. To