



Mini Review

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Biochemical and Molecular Genetic Predictors of Genital Prolapse



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Abstract

Objective: To study the presence of gene polymorphisms of extracellular matrix structural components and metabolism enzymes, receptors activity and mechanisms of intracellular regulation of the connective tissue in women with genital prolapse.

Subjects and methods: Analysis of published data on genetic polymorphisms and biochemical mechanisms of genital prolapse is presented.

Results: The paper presents the morden data on the impact of genetic polymorphisms on genital prolapse predisposition. It describes appropriate molecular genetic and biochemical processes of pathological connective tissue formation of pelvic organs and the pelvic complex in women with genital prolapse.

Conclusion: Genital prolapse is a multifactorial pathology with various pathological both extra- and intracellular mechanisms. At the moment, a lot of genetic variants are not specific only for this disease. There is no uniform consensus on the pathogenesis of the disease. Therefore, it is necessary to identify the specific molecular genetic markers of susceptibility to genital prolapse and identify high-risk groups, as well as the result prediction of surgical treatment.

Keywords: Genital prolapsed; COL3A1; FBLN5; LOX polymorphisms; Connective tissue dysplasia; TGF- β 1.

Introduction

Genital prolapse (GP) is a serious problem with high prevalence among the female population. It is due to adjacent organ dysfunction and a high rate of relapse after surgical treatment. The prevalence of GP varies from 4.5 to 30%. The risk factors of GP, such as increased abdominal pressure, difficult delivery, altered hormone imbalance, lead to abnormal remodeling of extracellular matrix. This disorder changes the normal architectonics and mechanical properties of pelvic floor tissues [1].

There is a hereditary predisposition to PG in 33% of cases. Genital prolapse is often accompanied by other clinical manifestations of connective tissue dysplasia [2]. The identification of genetic polymorphisms determining predisposition to GP are important.

Discussion

At the moment more than 30 genetic polymorphisms which can cause functional disorders of pelvic organs are described [3].

The expression of genes encoding the type I collagen alpha-1 and the type III collagen alpha-1 plays a key role in GP pathogenesis. The polymorphism of α 1 chain gene (*COL1A1*) is induced by the substitution of a guanidine residue to thymidine residue at the Sp1-binding site of the *COL1A1* gene [4]. This mutation leads to increased synthesis of RNA of the mutant allele and disruption of the normal structure of type I collagen. Type III collagen is an important factor in the repair of connective tissue. A single-nucleotide substitution in the coding region of type III collagen (*COL3A1*) showed to be a relevant risk factor for POP [5]. In this case alanine is replaced by threonine in all chains of the type III collagen. The structure of the whole helix changes and causes mechanical characteristic reduction and strength disruption of the pelvic floor.

Alarab et al. found that the expression of lxyloxidase (LOX) and lxyloxidase-like enzymes L1 and L3 (LOXL1, LOXL3) in vaginal tissue of women with pelvic organ prolapsed was significantly reduced [6]. These enzymes catalyze the processes

of collagen and elastin post-translational modifications. LOXL1 localizes specifically to sites of elastogenesis and interacts with fibulin-5. This process stabilizes the outer surface of cell walls and organizes elastin polymers into functional elastic fibers [7]. It has been shown that reduced expression of LOX, LOXL1 and LOXL3 genes can lead to connective tissue disruption and pelvic organ prolapse development [8].

In addition, single-nucleotide polymorphisms rs2018736 and rs12589592 of the fibulin-5 gene (*FBLN5*) determine predisposition to genital prolapse [9]. Fibulin-5 is secreted by endothelial cells, vessel smooth muscle cells, and fibroblasts. Fibulin-5 contains an evolutionally conserved arginine-glycine-aspartic acid (RGD) motif in the N-terminal region, which mediates binding to a subset of integrins, including $\alpha 5\beta 1$, $\alpha \nu\beta 3$, and $\alpha \nu\beta 5$. They are involved in intercellular interactions [10]. The reduction in *FBLN5* expression in vagina walls and pelvic organ ligaments decreases the expression of LOX enzymes and increases protease activity [11,12]. This leads to GP development and also increases the risk of GP recurrence after surgical treatment.

Missense mutations of a new locus WNK1 (with no lysine kinase) are involved in the pathogenesis of PG [13]. WNK1 protein a regulator of a variety of intracellular signaling pathways including the Wnt/ β -catenin pathway. The latter affects the formation of the mitotic spindle [14]. The mutation of the WNK1 locus causes a slow growth and proliferative activity of the fibroblasts in uterine ligaments and a decrease of collagen synthesis.

At the moment, the role of transforming growth factor beta-1 (TGF- $\beta 1$) in the pathogenesis of GP has been proven [15]. TGF- $\beta 1$ stimulate collagen synthesis enhancing extracellular matrix formation. The decreased expression of TGF- $\beta 1$ causes a decreased expression of connective tissue growth factor (CTGF) which leads to a slower growth and differentiation of fibroblasts and reduced synthesis of extracellular matrix components [16,17]. In parallel, the activation of matrix metalloproteinases (MMPs) and inhibition of tissue inhibitors of metalloproteinases (TIMPs) occurs. They cause increased fragmentation of fibers, aggravates the structural reorganization of connective tissue, reduces its strength and elasticity. This is manifested by the development of GP and stress urinary incontinence [18].

Another mechanism is the induction of expression of lysyloxidase-like enzyme-4 (LOXL4). The TGF-beta1 regulation of *LOXL4* expression is mediated through the binding of AP1 transcription factor to a conserved region of the promoter. This enzyme potentiates the processes of post-translational modifications of collagen and elastin, LOXL4 also suppresses the activity of MMP2. LOXL4 may function as a negative feedback regulator of TGF-beta1 in cell invasion by inhibiting the metabolism of extracellular matrix components that leads to an increased risk of GP [19].

Conclusion

Thus some of the mechanisms of genital prolapse development have been identified. However, there are many counterarguments regarding the pathogenesis of GP. The detected genetic variants are non-specific only for this disease. It is necessary to determinate predictors of GP and effective treatment modes.

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