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Review Article

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## Molecular effect of Leiomyomas

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### Abstract

Uterine leiomyomas, also called uterine fibroids or myomas, represent one of the most common benign tumor types in women of fertile age. Leiomyomas arise due to the transformation of the layer of smooth muscle cells of corpus uteri – themyometrium. Despite the frequent occurrence of this disease, the molecular mechanisms behind the origin and development of leiomyomas are still relatively unknown. Genetic factors also have an important impact on the development of these hormone-dependent tumors. However, the clinical and molecular characteristics of familiar and sporadic leiomyomas can widely differ. The main reason is the heterogeneity of this disease and the abundance of factors that can underlie their tumorigenesis. Clinical diagnosis of uterine leiomyomas without surgical interference can be hindered in the case of small, mostly submucosal leiomyomas or if it is necessary to avoid potential malignancy of the tumor. The main goal of this article is to summarize known facts about the etiology of leiomyomas and knowing molecular-genetic aberrations connected with the presence of leiomyomas.

**Keywords** Leiomyomas, uterine fibroids, tumourigenesis.

### Introduction

Uterine leiomyomas are the most common tumor type in pelvic minor with prevalence reaching up to 60% of women in their reproductive years (Baird et al., 2003). The prevalence increases with age, peaking in women in their 40s. Leiomyomas arise due to monoclonal transformation of smooth muscle cell layer of uterus, myometrium, and consist of large amounts of extracellular matrix (ECM) that contain collagen, fibronectin, and proteoglycan (Sankaran and Manyonda, 2008). Leiomyomas remain in almost 60% of cases asymptomatic, nonetheless, it is possible to expect that this number could be even bigger, because worldwide there still remains a large subset of undiagnosed women, mostly in developing countries. Furthermore, in many cases, uterine leiomyomas are diagnosed incidentally on clinical examination or imaging. Clinical presentation can lead to a decrease in quality of life and includes dysmenorrhea, pelvic

pain, menorrhagia, infertility, and complications during pregnancy. The complications include should erdystocia, abnormal postnatal bleeding, ectopic pregnancy, or even miscarriage (Gupta et al., 2008).

#### Molecular-genetic background of tumourigenesis of leiomyomas

Our knowledge about the genetic background of the tumourigenesis of uterine leiomyomas can be considered quite imbalanced. There are known relatively large packs of aberrantly expressed genes, among which important oncogenes and tumor-suppressor genes are present (Skubitz and Skubitz, 2003; Arslan et al., 2005; Wu et al., 2002). In any case, even notable aberrant expression of these genes should not be passably used as a typical sign of tumouri genesis of leiomyomas, because a lot of other factors can trigger these differences. Nonetheless, due to the monoclonal origin of

leiomyomas, there can be differences in gene expression between two leiomyomas that originated in the uterus of one patient. Different studies have established that about 40% of leiomyomas include some cytogenetic mutation. Some of these mutations cannot be considered as random but as leiomyoma-specific. Thus, a particular aberration could be connected with a particular abnormality in leiomyoma (Rein et al., 1991).

The most frequent aberration presented in leiomyomas is a rearrangement of 12q14-15, and within this group, translocation t(12;14)q15;q23-24) dominates. Quite often is also a paracentric inversion. This particular translocation affects the expression of the HMGA2 (Velagaleti et al., 2010). This gene is evolutionarily highly conserved and belongs to the non-histone chromosomal high-mobility group A protein family. Members of this family are able to regulate transcription without the need for any structural changes in DNA strains. In other words, they act as factors that allow other regulatory proteins to bind to their targets sequence (Fusco and Fedele, 2007). While the expression of HMGA2 is abundant in developing tissues, in healthy differentiated adult tissues it is minimal (Gross et al., 2003). In the case of uterine leiomyomas with mentioned translocation, HMGA2 is usually over-expressed. Particularly, in this case, chromosomal breakpoints have been assigned to regions outside the open reading frame of HMGA2 gene, thus primarily affecting its expression, rather than its protein sequence (Klemke et al., 2009).

Another, quite usual aberration is translocation 14q24 which affects functionality of RAD51B gene (Ingraham et al., 1999). The product of this gene, as a member of RAD51 family, is essential for DNA repair by homologous recombination (Date et al., 2006). Coupled rearrangements between this locus and HMGA2 in leiomyomas have been also observed (Schoenmakers et al., 1999).

### **Mutations and Aberrations**

The most common deletion in uterine leiomyomas is an interstitial deletion of chromosome 7-7q22. This deletion appears in about 7% of leiomyomas with aberrant karyotype (Sandberg, 2005). In this case, it is a bit harder to assess particular genes that are affected, because this region is considered to be gene-rich, this means that within its sequence, several different genes are encoded which can be affected independently based on the span of the mutation<sup>(16)</sup>. Notwithstanding, CUX1 is considered in this case as (at least very potentially) affected gene, which plays an important role in the regulation of transcription. This deletion usually occurs simultaneously, but some-times also together with t(12;14)(q15;q23-24) (Mehine et al., 2013).

Typical for these sole deletions is that leiomyomas are much smaller in size<sup>(14)</sup>. Rearrangements of 6p21 occur in less than 5% of karyotypically abnormal tumors. This type of rearrangement is in leiomyomas represented mostly by translocations occasionally involving 14q23-24 and inversions. In this regard, the HMGA1 gene is very often disrupted. This

gene belongs to the same gene family as HMGA2, thus contributing to the proper regulation of transcription<sup>(17)</sup>. HMGA1 expression is less affected, due to this aberration when compared to change in the expression pattern of the translocated HMGA2 gene (Somberger et al., 1999).

Different, less frequent aberrations connected with the development of leiomyomas are trisomy of 12, (Vanni et al., 1992) which can also probably in its final effect up-regulate the expression of HMGA 2, and monosomy of chromosome 10 (Sandberg et al., 2005). Furthermore, translocation within chromosome 10 (10q22) may affect regular transcription of KAT6B gene, which encodes one of the histone-acetyl transferase types (Moore et al., 2004). Besides the mentioned cytogenetic abnormalities, there is also a well-established knowledge about the impact of common low-penetrance risk variants in susceptibility to leiomyomas, which were achieved as a result of genome-wide association study (GWAS) examinations. After all, there can be discrepancies in the attempts to replicate previously achieved associations that are conducted by a different group of authors. Anyway, this can be caused due to the heterogeneity of leiomyomas in many aspects; in other words, tumorigenesis of leiomyomas can be dependent on a pack of multiple variants with a small effect.

The very first wide and broad analysis was performed by Cha et al., 2011. The authors, after genotyping of more than 1600 patients from Japan, found three loci that were especially predisposed to structural changes among patients with leiomyomas. These loci were 10q24.33, 22q13, and 11p15.5. For the chromosome 10q24.33 region that showed the most significant association with uterine fibroids, the associated region was mapped to the S' region of SLK and OBFC1. Importantly, SLK gene encodes STE20 kinase (Cha et al., 2011) which has a crucial impact on myogenic differentiation. For the chromosome 22q13.1 region, SNPs showing strong associations with uterine fibroids were mapped within a 200-kb linkage disequilibrium (LD) block, encompassing TNRC6B (trinucleotide repeat-containing gene 6B), encoding a component of the messenger RNA (mRNA)-degrading cytoplasmic processing (P) bodies that play a critical role in microRNA (miRNA)-mediated gene silencing and small interfering RNA-dependent endonucleolytic cleavage of complementary mRNAs. In the GWAS study of the European female population (Eggert et al., 2012), there was found another novel significant locus on chromosome 17q25.3, two significant linkage peaks on chromosomes 10p11.21 and 3p21.31 and then five suggestive peaks on chromosomes 2q37.1, 5p13.3, 11p15.5, 12q14.1 and 17q25.3. 17q25.3 spans fatty acid synthase (FASN), coiled-coil-domain-containing 57 (CCDC57), and solute-carrier family 16, member3 (SLC16A3).

Uterine leiomyomas are often accompanied by certain hereditary cancer-related syndromes, for instance, hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome (Zhang et al., 2015; Wise et al., 2012). Leiomyomas are associated with the explicitly specific traits of this syndrome, such as the early age of onset, higher prevalence, or a large nucleus with a prominent eosinophilic nucleolus

surrounded by a clear halo (Wise et al., 2012). HLRCC is caused by the heterozygous germline mutations of the fumarate hydratase (FH) gene (Chang et al., 2015). X-linked Alport syndrome is also statistically associated with a more frequent occurrence of leiomyomas. Alport syndrome arises due to defects in COL4SA and COL46A genes (Lehtonen, 2011). Uterine leiomyomas are many times manifested together with Cowden syndrome, which is associated with defects in the PTEN gene (Tomlinson et al., 2002), or with Schwannomatosis, which is associated with defects in SMARCB1 gene (Uliana et al., 2011). The presence of leiomyomas spotted together with Gorlin syndrome (causative gene PCH1) (Waite et al., 2002) or Tuberous sclerosis (causative genes TSC1, TSC2) is less often (Hulsebos et al., 2014). In either way, due to the high frequency of sporadic leiomyomas, it is necessary to take into account that simultaneous occurrence is often only a result of mere coincidence.

### **Pathogenesis of leiomyomas**

The study of the pathogenesis of leiomyomas and their ECM has demonstrated that one of the most susceptible factors involved in this activity's changes is transforming growth factor- $\beta$  (TGF- $\beta$ ) (Garavelli et al., 2014). Particularly, the subunit 83, which is the only isoform expressed in mesenchymal cells, and its signal mediators are usually up-regulated (Hancock et al., 2002). Also, the activity of this factor can negatively affect the activity of other growth factors (Garavelli et al., 2014). No matter whether affected by TGF- $\beta$  or not, the activity of several other growth factors, or their receptors, has been observed to be changing when leiomyomas have been presented.

These are, namely, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), human heparin-binding epidermal growth factor-like growth factor (hHIEBEGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), transforming growth factor- $\alpha$  (TGF- $\alpha$ ), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) (Kogan et al., 2005).

bFGF and VEGF contribute to increased levels of angiogenesis. EGF and PDGF positively modulate the synthesis of DNA via transient activation of different types of kinase pathways (Norian et al., 2009). The previously mentioned TGF- $\beta$  can affect the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase (ERK)/Smad signaling pathway, which can result in modulation of expression of various types of genes. Finally, it is intriguing that the gene encoding this subunit is localized closely to 14q23-24 breakpoints – one of the most common translocation sites identified in cytogenetic studies of fibroids. Unfortunately, there is a lack of connections between these two factors in the case of leiomyomas. It would be of great benefit to estimate whether upregulation of TGF- $\beta$ 3 can potentially occur as a result of disruption of regulatory elements due to the translocation events, similarly as in the case of HGM2 overexpression, or due to the somatic mutations unaffected by chromosomal rearrangements, as in

the case of arrhythmogenic right ventricular cardiomyopathy (ARVC)-type disease (Arita et al., 2005).

Nowadays, the gene MED12 (mediator complex subunit12) can be marked as a typical leiomyomas phenomenon, due to the mutations of this gene in almost 70% of fibroids with normal karyotype in patients from various ethnic and racial groups. The percentage was established as an outcome of whole-exome sequencing approaches (Ren et al., 2011; Rampazzo, 2006; Perot et al., 2012). Notably, this mutation is also present in smaller proportions, within leiomyosarcomas, in about 10% of the cases, and in small portions of STUMPs (Mäkinen et al., 2011). Nevertheless, this mutation can be still considered as strictly typical for leiomyomas. Comparably, even there were observed different mutations of this gene the clear majority of MED12 mutations consist of missense mutations at codon 44, especially the amino acid change G44D (McGuire et al., 2012). Finally, MED12 has been shown to physically and functionally interact with b-catenin, the key effector of canonical Wnt signaling, to activate transcription of the target genes (Bertsch et al., 2014). MED12 is also essential for embryonic development and its deletion disrupts both canonical Wnt signaling and Wnt/PCP3 (Markowski et al., 2012).

A second somatic mutation, relatively typical for leiomyomas, can be considered a mutation in FH gene. However, even aberrations in this gene are more likely to be associated with the deletions 14q33 or are considered as sporadic for HLRCC syndrome, and somatic mutations can be found in a smaller subset of nonhereditary leiomyomas. Particularly, based on immunohistochemistry (IHC) leiomyoma staining and subsequent MPS as well as Sanger sequencing approaches, 1% of all uterine leiomyomas should be FH deficient due to somatic inactivation (Moore et al., 2004).

### **Conclusion**

Uterine leiomyomas are nowadays the most frequent indication to perform hysterectomy. Hysterectomy, or at least myomectomy, is still roughly the only method that can in combination with consequent histopathological examinations provide sufficient information about the potential malignancy of tumors. Leiomyomas as a tumor type of monoclonal origin form a very heterogeneous group and even though heterogeneity can be widely observed in their etiology and pathogenesis, the most heterogeneous feature is the genetic background of these tumors. In particular, tumors within the same uterus can be accounted for by aberrations in different genes, while tumors from two non-related patients can have almost identical defects.

### **Conflict of Interest**

The author hereby declares no conflict of interest.

### **Consent for publication**

The author declares that the work has consent for publication.

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