

The structure of the cytokine gene network in uterine fibroids

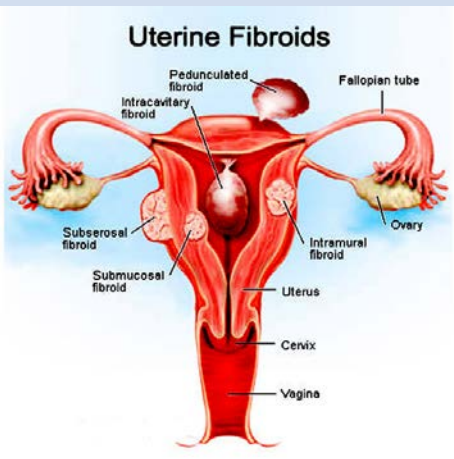
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INTRODUCTION

Uterine fibroids (UF) is one of the most common benign monoclonal tumors of the female reproductive system with a high prevalence worldwide - from 20 to 77% in different regions. Very often, UF is a risk factor for decreased fertility or even infertility.

The development of UF is associated with complex heterogeneous hormonal, genetic and epigenetic factors, impaired functions of various cytokines, chemokines and growth factors, which function as part of the “cytokine network”.



Since the activity of this network, in turn, is coordinated by the “cytokine gene network”, it is very relevant to study the features of its structural organization to understand the pathogenesis of UF development.

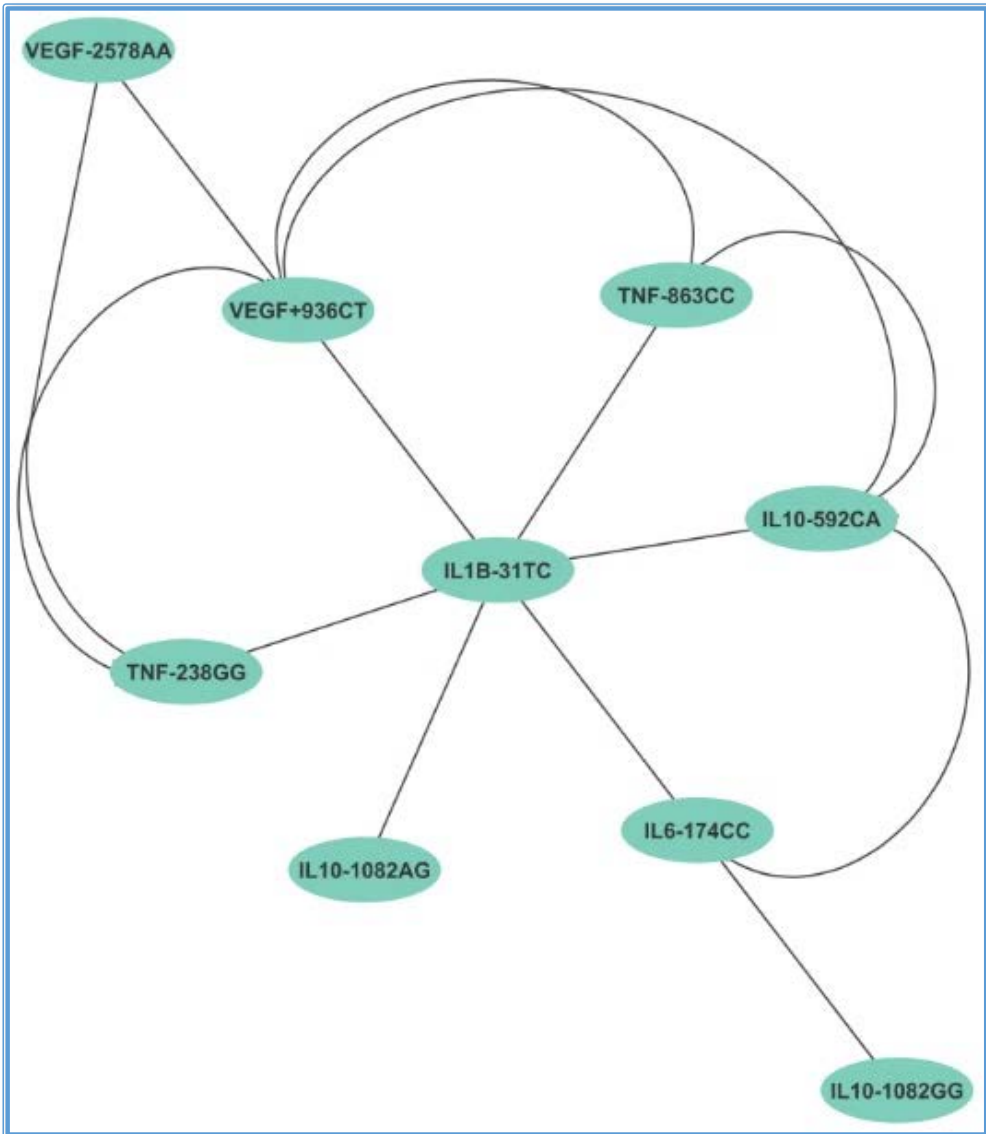
PATIENTS AND METHODS

The study included 36 patients of Caucasian origin with a verified diagnosis of UF who underwent surgical treatment in the volume of laparoscopic myomectomy. The age of the patients ranged from 23 to 54 years. In the control group were 75 healthy women of similar age. Investigated 12 SNPs in the promoter regions of cytokine genes: TNFA -238 A/G, -308 A/G and -863 C/A, IL1B -31 C/T, IL4 -590 C/T, IL6 -174 C/G, IL10 -592 C/A, IL10-1082 A/G gene growth factor vascular endothelial VEGF+936 C/T, VEGF -2578 C/A, genes of matrix metalloproteinases MMP2 T/C, MMP9 C/T. Study of the polymorphism was performed by the method of RT-PCR.

The visualization of pairwise gene-gene interactions in groups with and without UF in the form of an interactive biological network was carried out in the Cytoscape program v.3.7.2.

The interpretation of the visualization results was based on the general global and local topological properties of biological networks.

A FRAGMENT OF THE GENE NETWORK OF CYTOKINES IN UTERINE FIBROIDS



THE MAIN CYTOKINES GENES BY UF DEVELOPMENT

Polymorphic genes	Frequency (%)
IL1B-31 TC	20.0 (8.4 – 39.1)
VEGF+936 CT	16.7 (6.3 – 35.5)
IL10-592 CA	13.3 (4.4 – 31.6)
IL6-174 CC	10.0 (2.6 – 27.7)
TNF-238 GG	10.0 (2.6 – 27.7)
TNF-863 CC	10.0 (2.6 – 27.7)
VEGF-2578 AA	10.0 (2.6 – 27.7)
IL10-1082 GG	6.7 (1.2 – 23.5)
IL10-1082 AG	3.3 (0.2 – 19.1)

THE VARIANTS OF PAIR INTERACTIONS OF CYTOKINES GENES AT UF

Pair interaction	Genotypes	Frequency (%)
IL1B-31:IL10-592	TC-CA	13.5 (10.4 – 17.3)
TNF-238:IL1B-31	GG-TC	12.0 (9.0 – 15.7)
IL1B-31:IL10-1082	TC-AG	10.5 (7.7 – 14.0)
TNF-863:IL1B-31	CC-TC	9.7 (7.1 – 13.2)
TNF-238:VEGF+936	GG-CT	9.0 (6.5 – 12.3)
IL10-592:VEGF+936	CA-CT	7.7 (5.4 – 10.9)
TNF-863:IL10-592	CC-CA	7.7 (5.4 – 10.9)
TNF-863:VEGF+936	CC-CT	5.2 (3.4 – 8.0)
IL6-174:IL10-592	CC-CA	5.0 (3.2 – 7.7)
TNF-238:VEGF-2578	GG-AA	4.7 (3.0 – 7.4)
IL1B-31:VEGF+936	TC-CT	4.5 (2.8 – 7.1)
IL1B-31:IL6-174	TC-CC	4.0 (2.4 – 6.5)
IL6-174:IL10-1082	CC-GG	4.0 (2.4 – 6.5)
IL10-1082:VEGF-2578	GG-AA	1.5 (0.6 – 3.4)

= CONCLUSION =

The analysis of the gene network topology, which submitted in this figure, has allowed us to allocate the main genes and the main intergenic interactions which bring the greatest contribution to development UF. In our opinion, 3 polymorphism can act as the main genes: *IL1B-31 TC*, *VEGF+936 CT* and *IL10-592 CA*.

These genes form the basic units in the genic network as have the greatest quantity of interactions with other genes. These polymorphisms form the main intergenic interactions: [*IL1B-31 TC: IL10-592 CA*] (13.5 %), [*TNF-238 GG: IL1B-31 TC*] (12.0 %), [*IL1B-31 TC: IL10-1082 AG*] (10.5 %), [*TNF-863 CC: IL1B-31 TC*] (9.7 %), [*TNF-238 GG: VEGF+936 CT*] (9.0 %) on which share it is necessary 55 % from the all basic interactions in the genic network which are associated with UF development.

► This topology of the gene network ensures balanced flow of angiogenesis processes, the functioning of the extracellular matrix and the processes of inflammation in the myometrium, which prevents the development of uterine fibroids.