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Review Article

The Role of The βklotho Gene, Fgf21 and Fgfr1 in Cancerogenesis.

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Abstract

Klotho was discovered in 1997 as an anti-aging gene that, when overexpressed, may extend the life span, but when it is disrupted, it may be a factor responsible for premature aging syndrome. The structure and the role of αKlotho and βKlotho genes from Klotho family in malignant tumors is described. The expression profile of the βKlotho gene is significantly different from the expression of the αKlotho gene. Analysis of Klotho expression in breast cancer, cervical cancer as well as endometrial cancer are discussed. The available data indicate the involvement of βKlotho in the neoplastic transformation of the endometrium. More advanced disease is related to negative expression of βKlotho gene. Fibroblast growth factors (FGFs) are a large family of proteins characterized by different functions in the cell development and metabolism. The FGF signaling is also associated with cancerogenesis. The relation between some FGF subfamilies and endometrial cancer clinical data is reported. The interaction between FGF subfamilies and the Klotho subfamily proteins acting as a co-receptor is stressed.

Disorders in signaling of the FGF / FGFR pathway have been confirmed in gynecology. It can be assumed that increased expression of FGF21 might be a suppressor factor in endometrial cancer. The FGF21 factor, like the βKlotho protein, achieves its biological effect via the FGFR1 receptor. High expression of the FGFR1 gene inhibits further tumor growth. FGFR1 has the potential to perform both a suppressor and promoter role in the oncogenesis process.

Keywords: βklotho gene, fgf21, fgr1, endometrial cancer, cancerogenesis

Introduction

Significant progress in molecular biology caused a growing interest in searching for genetic background of malignant diseases. One of the most important features connected with neoplasmatic tumor growth is its immortality. The list of genes which play a role in the process of immortalisation is growing constantly. One of the most influencing genes responsible for the malignant cell life span is the Klotho family. The fibroblast growth factor (FGF) is another protein family involved in cell survival, proliferation and migration. The FGF family activation is moderated by the betaKlotho protein which plays a role of co-receptor necessary for FGF functioning in the cell. Thus, the relation between those two proteins in malignant tumors is still under investigation.

The structure of the gene and protein βKlotho

Klotho was discovered in 1997 as an anti-aging gene that, when overexpressed, may extend the life span, but when it is disrupted, it may be a factor responsible for premature aging syndrome [1, 2]. The name of the gene and protein is derived from the Greek goddess Klotho, who along with the sisters Lachesis and Atropos spun the thread of human life and decided on its length [3, 4].

Klotho is composed of 1014 amino acids and has at its N-terminus signal sequences and the intra-membrane domain and short cytoplasmic domain at the C-terminus. The Klotho part of the trans membrane segment consists of two repeats (KL1 and KL2) that divides the homology sequence with β-glucosidase (Figure 1) [5].

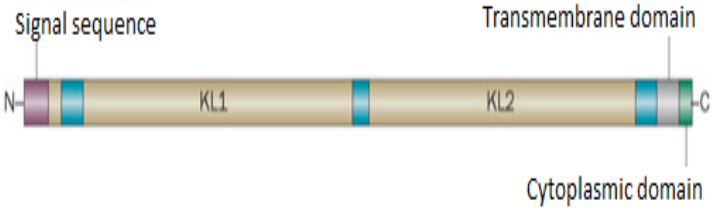


Figure. 1 Diagram of the Klotho protein structure (developed on the basis of UniProt Knowledgebase).

Based on the similarity of the human DNA sequence to the sequence corresponding to αKlotho in mice, another 2 genes belonging to the Klotho family, βKlotho andIntrodusc γKlotho which is called KLPH (KL lactase phlorizin hydrolase) or LCTL (lactase-like protein) [6].

The βKlotho (KLB) gene encoding the monotopic transmembrane protein was discovered in 2000 as a homologue of the αKlotho gene (αKL) of mice (4). The human KLB gene, 44.68 kb in length, is located in the region 1 of the band 4 of the short chromosome 4 (4p14) and, similarly to the mouse, it consists of 5 exons and 4 introns. The mature transcript of this gene reaches a length of 6.08 kb [7-9].

The expression profile of the βKlotho gene is significantly different from the expression of the αKlotho gene. Studies in the mice KLB show that the expression of this gene is closely related to the metabolism of cholesterol and bile acids, and the presence of βKlotho protein in the pancreas, fat tissue and liver suggests that this protein may play a much wider role in metabolism (10), (11).

In humans, KLB expression was detected mainly in the liver, fat tissue, glandular tissue of the breast and also in the spleen, testes, prostate, eyeball and brain [8] (Fig. 2).

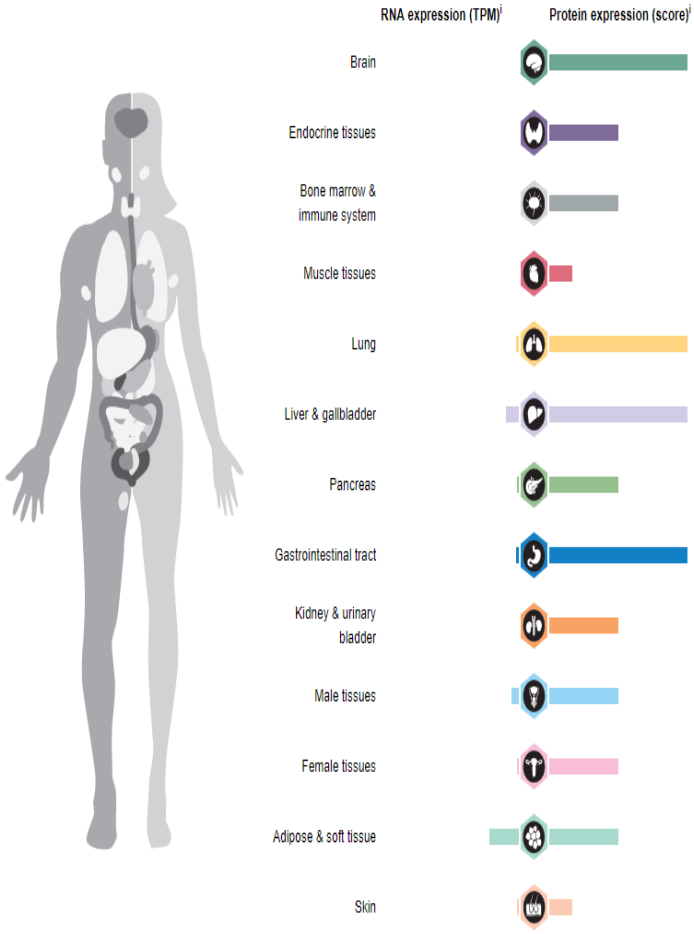
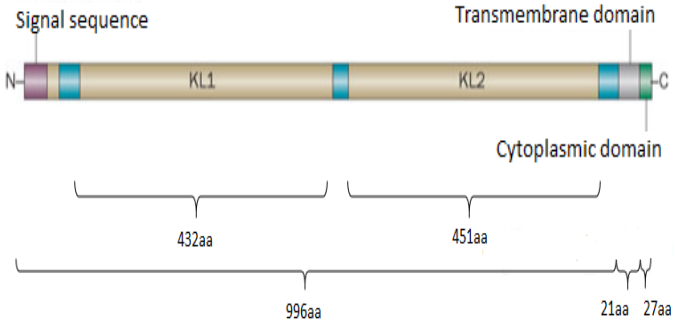


Figure .2 Expression of the βKlotho gene and βKlotho protein in the human body (12).

βKlotho protein

The trans membrane protein βKlotho has a molecular mass of 119.8 kDa and is a homologue of the αKlotho protein. The level of amino acid compatibility between these proteins in humans is about 41.2% (86) As in the case of αKlotho protein, there are two repeated regions in the extracellular domain of βKlotho with structural similarity to one family of glycoside hydrolases (Figure 3) [4, 13, 14].



There are also important facts that distinguish βKlotho from its αKlotho homologue. Unlike αKlotho, previous studies have not shown that the βKlotho gene transcript undergoes an alternative assembly process that would result in the secretion of this protein. Also it does not seem that, as in the αKlotho protein, in the βKL2 region there was a short amino acid sequence KKRK, within which the protein would be proteolytically cleaved [13].

βKlotho

The Klotho gene is considered to be the youth gene (1) (2). The role of the Klotho gene transcript in the process of cancer is of great interest to scientists and has been studied so far in many malignant diseases. Immuno histochemical analysis of Klotho expression in breast tissue showed its high expression in healthy tissue and very low gene expression in breast cancer tissue. In tissue samples of breast cancer, high Klotho expression was correlated with a smaller tumor size and less mitotic activity. Detailed studies of breast cancer cells have shown that the Klotho gene as an inhibitor of the IGF-1 pathway (insulin-like growth factor-1) and also an activator of the FGF pathway (fibroblast growth factors) is a tumor suppressor [15].

Cervical cancer studies have shown that Klotho mRNA is absent in numerous samples of cancer tissue at advanced FIGO stages, but not in early pre-invasive (*in situ*) oncogenesis. After treatment, Klotho's expression returned to normal. Therefore, it was concluded that the reduction of Klotho expression may be highly advanced in cervical cancer. The βKlotho gene from the Klotho family is also the object of interest of many scientists. The first data on this gene confirmed its role in the development of liver cancer. Then the study of the role of βKlotho in the progression of liver cancer gave divergent results [16, 17]. However, most studies suggest that βKlotho inhibits the proliferation of liver cancer cells. According to Poh et al. [16], increased expression of βKlotho and FGFR4 was detected in human liver cancer cells. A similar increase in expression was observed in HCC cell lines (hepatocellular carcinoma). This suggests that increased expression of KLB is associated with neoplastic transformation and progression of liver cancer. On the other hand, other data showed reduced KLB expression in HCC and HCC cell lines [17]. In addition, restoration of normal KLB expression in these cells inhibited their proliferation.

Until now, the level of KLB expression has been marked in various healthy and cancerous tissues (Figure 4).

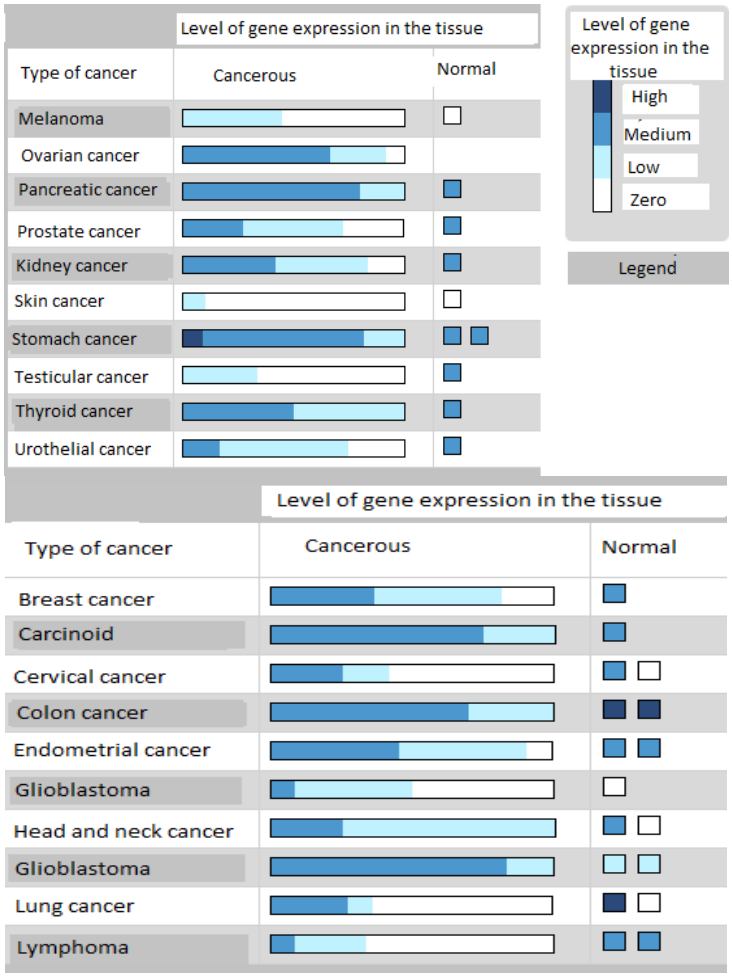


Figure. 4 Graphic presentation of KLB gene expression in healthy and cancerous tissue based on (18).

Presented data clearly support a different expression of the examined gene in normal and tumor-altered tissues. In endometrial cancer, KLB expression is low or negative, whereas in healthy endometrial tissue the expression value is determined at the medium level.

The available data clearly indicate the involvement of βKlotho in the neoplastic transformation of the endometrial mucosa, and encourage further analysis.

Recently published studies (63) on endometrial cancer correlate the βKlotho with the clinical FIGO stage, the lymph node involvement and the cellular differentiation of the tumour (grading).The higher (3 or 4) FIGO stages occur almost exclusively when the expression of the βKlotho gene is 0. When the gene expression is higher than zero, the most cases (about 90%) were observed in FIGO stage 1. Moreover, in the G3 cases, the value of βKlotho gene expression assumes only the value equal to 0. Gene expression in the G2 tumours assumes the whole range of values with a clear predominance of values of 0. In contrast, in the grade G1 tumor the highest gene expression values are the predominant. The lymph node involvement is observed when the expression of the βKlotho gene is equal to 0, whereas in the majority of cases (97%), the lymph nodes are not involved when the βKlotho gene expression is positive. These data may indicate that the negative expression of the βKlotho gene promotes the promotion of neoplastic process in endometrial cancer. In opposite, high expression of the βKlotho gene may play a suppressor role in the neoplastic transformation of the endometrium.

FGF fibroblast growth factors - structure and functions

Fibroblast growth factors (FGFs) are a large family of proteins characterized by different functions in the development and metabolism of the cell. They regulate proliferation, differentiation, survival and migration of cells, their resistance to drugs as well as angiogenesis and wound healing [19, 20]. The signaling of growth factors is also associated with pathological conditions such as cancer and metabolic diseases [21, 22]. The human FGF family consists of 22 proteins (FGF1-FGF23) and using phylogenetic analysis and gene locus, fibroblast growth factors can be divided into seven subfamilies, and the composition of each is presented in .

Subfamily	Proteins
FGF1	FGF1, FGF2, FGF5
FGF3	FGF3, FGF4, FGF6
FGF7	FGF7, FGF10, FGF22
FGF8	FGF8, FGF17, FGF18
FGF9	FGF9, FGF16, FGF20
FGF11	FGF11, FGF12, FGF13, FGF14
FGF15/19	FGF15/19, FGF21, FGF23

Table 1.

Based on the mechanism of their operation, these sub-families can be classified into three families [21, 24, 25]: Intracrine family - FGF1 subfamily. The proteins is active inside the cell in which is synthesise. For its activity they do not need FGFR receptors and interaction with heparin / heparan sulfate. They participate in the functioning of neurons during postnatal development [26, 27, 28].Paracrine family - 5 subfamilies: FGF1, FGF3, FGF7, FGF8 and FGF9. These proteins act as locally secreted signal molecules and are involved in various developmental processes, such as cell differentiation, proliferation and migration as well as angiogenesis and wound healing. They require appropriate FGFR and heparin / heparan sulfate [29] to be effective [30].Endocrine family -subfamily FGF15 / 19. It is a relatively new group of proteins found only in vertebrates. These proteins are quite unusual. Their biological response depends on FGFR, but they interact poorly with heparan sulphate and heparin. To strengthen the interaction with the receptor, other co-receptors from Klotho family are needed, respectively: αKlotho proteins for FGF23 and βKlotho for FGF15 / 19 and FGF21. Representatives of this FGF family can penetrate cells and tissues into the bloodstream, thus affecting distant tissues and organs in the endocrine way.

These proteins have metabolic activity including regulation of bile acid synthesis, carbohydrate and lipid metabolism as well as phosphate, calcium and vitamin D homeostasis [31-35].

FGF-21

The fibroblast growth factor 21 (FGF21) belongs to the family of the endocrine fibroblast growth factors. The FGF21 gene was originally isolated from the genetic material of mice by PCR (*polymerase chain reaction*) with the amino acid sequences of the human FGF15 / 19 gene. The human FGF21 gene has been identified byhomologous screening of the human genome [36]. Expression of FGF21 mRNA was confirmed mainly in the liver, pancreatic β islet cells and testes [36, 37]. Lower levels of expression are also observed in the thymus, fat tissue, duodenum [11], skeletal muscle and pancreatic β-cell cells [37, 38] (Fig. 5).

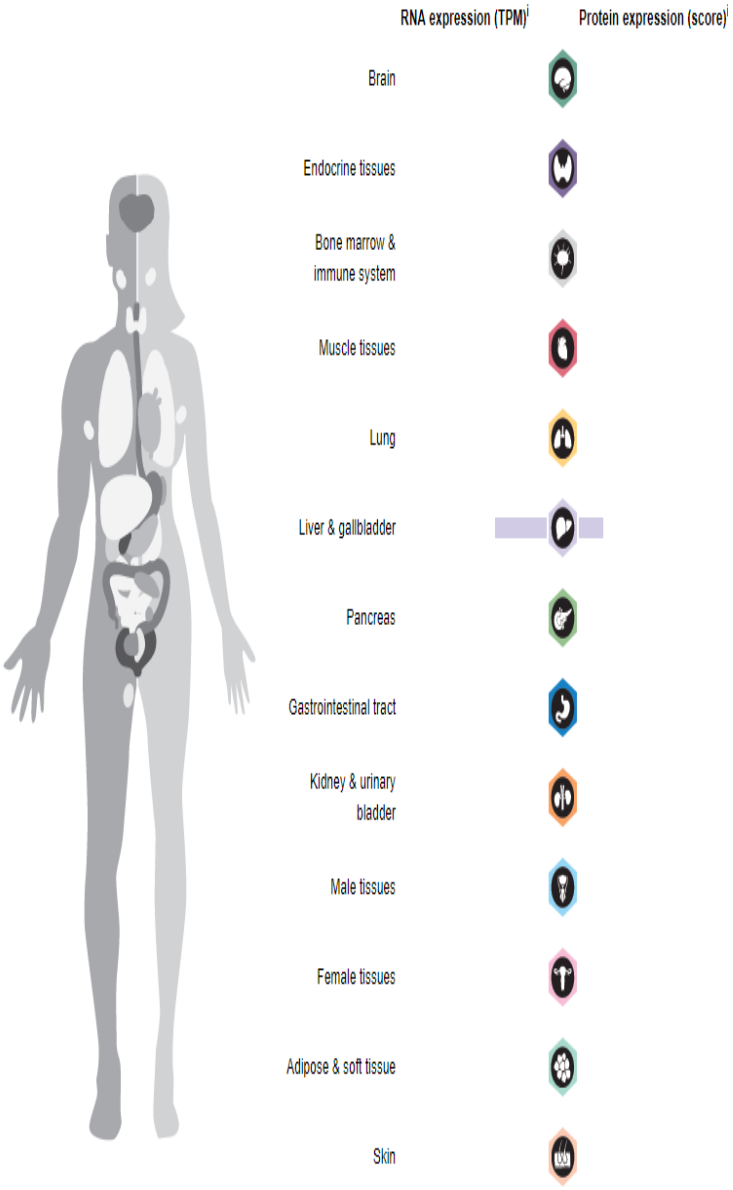


Figure. 5 Expression of the FGF21 gene and FGF21 protein in the human body (12).

The FGF21 gene is located in the region 5 of chromosome 19. Studies have shown that with obesity caused by both genetic factors and abnormal diet, the activity of the studied growth factor FGF21 induces a reduced level of glucose and insulin in the blood, a change in the lipid profile with a significant reduction in LDL and cholesterol levels.

the benefit of HDL and consequent weight loss through increased energy expenditure without the need to reduce meals [39].

In summary, the functions of FGF21 in many aspects is similar to the role of insulin (Table 2).

Effect	insulin	FGF21
Glucose uptake	↑	↑
Levels of triglycerides	↓	↓
Level LDL – c	↓	↓
Level HDL – c	↑	↑
Lipogenesis	↑	↑
Ketogenesis	↓	↑
Body weight	↑	↓
The level observed with insulin resistance	↑	↑
The level observed with metabolic diseases	↑	↑
Level in diabetes	↑	↑

Table 2. Comparison of the effects of insulin and FGF21 in the energy balance, and metabolism of lipids and carbohydrates (40)

Receptors of FGFR fibroblast growth factors - structure and functions

Receptors for fibroblast growth factors (FGFRs) are monotopic transmembrane proteins with tyrosine kinase activity [41].\Data from the literature indicate that proteins belonging to the FGF15 / 19 subfamily (including FGF21) have an extremely low affinity for FGFR. To achieve the greatest ability to bind to and activate the receptor,the

FGF15 / 19 subfamily proteins must interact with the Klotho subfamily proteins acting as co-receptors [43-45].Co-operation of βKlotho with FGF21 and FGFR1Endocrine growth factors, among them FGF21, provide a biological cellular response depending on growth factor receptors (FGFR). The activity of FGF21 against FGFR is low even in the presence of heparin or heparan sulfate [46, 47]. To obtain a metabolic cellular effect, FGF21 requires the presence of βKlotho protein [48]. The impulse to transmit the FGF21 signal is a complicated process of creating a triple complex between FGFR1, βKlotho and FGF21.

FGFR1c may remain inactive despite the close presence of βKlotho in the absence of FGF21 [49]. Only the combination of FGF21 and βKlotho leads to the dimerization of FGFR1c in a manner allowing activation of the signal [50]. FGF21 and βKlotho act synergistically, increasing their chances of joining the receptor and thus obtaining a biological effect [50]. In addition, FGF21 itself contains amino acids at the N-end that determine its affinity for FGFR. The removal of 6 amino acid residues from the N-end of FGF21 significantly reduces its activity, whereas the removal of 8 amino acids abolishes it completely [51].Latest reports are increasingly related to genetic aspects in the epigenesis of malignant tumors. The life cycle of the cell is controlled at the genetic level. The general scheme of carcinogenesis is based on the initiation of a genetic error, its promotion and progression. The process of apoptosis prevents the fixation of genetic errors. All this determines the search for mechanisms responsible for cancer at the

genetic level of a single cell.The available data indicate the relationship between the expression of βKlotho genes, FGF21 and FGFR1, which at the cellular level, by regulating the life cycle of the cell and activation of metabolic pathways, may decide on the promotion of carcinogenesis or suppression of cancer. In the endometrial cancer, indirect indicators of malignancy seems to be: the clinical FIGO stage, the lymph node

metastases and the tumor differentiation (grading). The analysis of the relation between the expression value of the examined genes and the mentioned above factors in a representative cohorts, indicate the important role of the examined genes in the cancerogenesis of the endometrium.

FGF / FGFR pathway signaling disturbances

Various aberrations of FGFR signaling have been identified in tumors:

FGFR1	Amplification	Breast (hormone sensitive)	10
		Lung (squamous cel carcinoma)	10-20
		Lung (small cel carcinoma)	6
		Head and neck (squamous cel carcinoma)	10-17
		Esophagus (squamous cel carcinoma)	9
		Ovary	5
		Osteosarcoma	5
FGFR2	Amplification	Breast	4
			5-10
	Mutation		12
FGFR3	Mutation		50-60
		Bladder (muscle-infiltration)	10-15
	Translocation	Bladder (muscle-infiltration)	6
		Glioblastoma multiformae	3-7
FGFR4	Amplification	Stomach	5
	Mutation	Endometrial	8
		Bladder (non-muscle infiltration)	

Table 3 : shows the FGFR gene aberrations most commonly found in solid tumors

Disorders in signaling of the FGF / FGFR pathway have also been confirmed in gynecology. Fibroblast growth factors and their receptors play an important role in the proper development and functioning of the breast glands. Over recent years, it has been demonstrated that ectopic expression of FGF / FGFR family proteins may induce cancer transformation in breast cancer [53]. An important role in the progression of breast cancer by signaling initiated by fibroblast growth factors is attributed to FGFR1. Amplification of this gene was observed in 10% of patients with breast cancer. Of the 880 analyzed breast tumor specimens, the increased expression of FGFR1 mainly concerned HER2 negative (human epidermal growth factor receptor 2) patients over 50 years. It has also been shown that the amplification of the FGFR1 gene in women with estrogen receptor-ER breast cancer increases the risk of distant metastases and is associated with the progesterone receptor deficiency [54, 55].

In ovarian cancer, the gene encoding fibroblast growth factor 3 (FGF3) is amplified. Amplification of FGF3 was demonstrated in 20% of 136 examined cases. In addition, analysis of the results showed a significant correlation between the number of copies of the FGF3 gene and the FIGO stage classification [56]. Other reports show that FGF3 is expressed only in cancerous tumor tissue whereas it is not present in normal tissue [57]. A similar relationship was also demonstrated in FGF19. In ovarian cancer tissue,

amplification of the 5q31 region including the FGF1 gene has also been identified. Increased expression of FGF1 at the level of mRNA and protein was also correlated with a higher level of angiogenesis marker i.e. cluster31 differentiation antigen. These data may therefore suggest that FGF1 enhances the process of angiogenesis, which in turn may be the cause of worse prognosis of patients with FGF1 amplification [54, 58].

FGF21

Current reports are focused on deeper analyzes of FGF / FGFR pathway disorders. The growth factor of FGF21, which is the co-receptor of KLB [48], plays an important role in carbohydrate-lipid cell metabolism and has a positive effect on weight reduction [59, 60]. Both carbohydrate-lipid disorders and obesity are well known as a risk factors of the endometrial cancer. That is the reason why it is so important to elucidate the role of FGF21 in the endometrial cancer. The evaluation of FGF21 gene expression indicates that the high expression of the FGF21 gene (above 70.2) is accompanied by a strong dominance of the lowest clinical stage FIGO (stage 1). The lower values of gene expression are in turn accompanied by a significant increase in the share of higher (2 or 3) FIGO stages. It can therefore be assumed that increased expression of FGF21 might be a suppressor factor in endometrial cancer. Similar results have been obtained in the most recent studies of liver cancer [61], where it was observed that the initially increased expression of FGF21 is a defense and compensatory mechanism.

However, in the late stage of changes taking place in the cell, the reduction of FGF21 expression may be associated with chronic liver disease, including neoplastic transformation. Considering the fact that obesity and diabetes associated with lipid disorders are common in patients with endometrial cancer, due to the associated reduction of FGF21 expression, these diseases are a direct risk factor for cancer development. Therefore, it can be assumed that patients with metabolic disorders are devoid of the protective effect of FGF21. As is known, in most solid tumors, including endometrial cancer, there are numerous hypoxic outbreaks in which a low oxygen concentration may contribute to the reduction or even loss of FGF21 exposures leading to tumor development. Nevertheless, the mechanisms for reducing or losing FGF21 expression in endometrial cancer are not fully understood. In addition, FGF21 factor is the regulator of many metabolic processes in tissues with intensive expression of KLB [62]. Therefore, the further studies in this issue are needed.

In endometrial tumors, there was no statistically significant relationship between the presence of lymph node infiltration and FGF21 gene expression. In the majority of cases, the lymph nodes were not affected. The expression value of the FGF21 gene assumes a full range both in the group of patients with cancer and in the control group. On this basis, the local role of FGF21 can be attributed to the development of endometrial cancer without affecting lymph node metastases. This relation requires further analysis in a larger group, possibly also the evaluation of FGF21 expression in the lymph nodes themselves, in order to assess its local impact [63]. The histological differentiation of the tumor is of great prognostic importance. Studies on histological grading dependence on the FGF21 gene expression value did not show significant relationships.

It is worth noting, however, that the expression of the FGF21 gene equal to 0 was not accompanied by a single case of endometrial cancer with a high tumor differentiation (G1) [63].

FGFR1

The FGF21 factor, like the βKlotho protein, achieves its biological effect via the FGFR1 receptor. Studies on the expression of FGFR1, depending on the clinical - histological factors of endometrial cancer, showed a strong relationship between the clinical andpathological data of the tumor and the expression of FGFR1 [63].High values of FGFR1 gene expression occur only at the lowest FIGO stage. In the higher clinical stages (FIGO 2 and 3) the majority of cases with lower FGFR1 expression were observed. It can be assumed that high expression of the FGFR1 gene inhibits further tumor growth. This is probably due to the protective effects of βKlotho and FGF21 proteins, which reach their biological effect via the FGFR1 receptor. The influence of FGFR1 expression on the degree of histological differentiation (grading) is similar. Tumors of unfavorable maldifferentiation (G3) were usually accompanied by low expression of FGFR1. In the group with higher expression of the studied receptor, the incidence of G3 tumors decreased significantly. It also seems that the expression of FGFR1 is associated with the risk of metastasis of endometrial cancer in regional lymph nodes. Although the majority of data related to patients with lymph nodes were free of neoplastic infiltration, at low values of FGFR1 gene expression in 1/3 of the cases, the lymph nodes were occupied, whereas with higher gene expression, in almost 95% of cases the lymph nodes were not affected. The question, whether high expression of FGFR1 also has a protective effect on the formation of distant metastases requires further research. In the available literature, data evaluating the effect of FGFR1 expression on the development of endometrial cancer is limited [63]. FGFR1 expression was assessed in many tumors (Fig. 9),

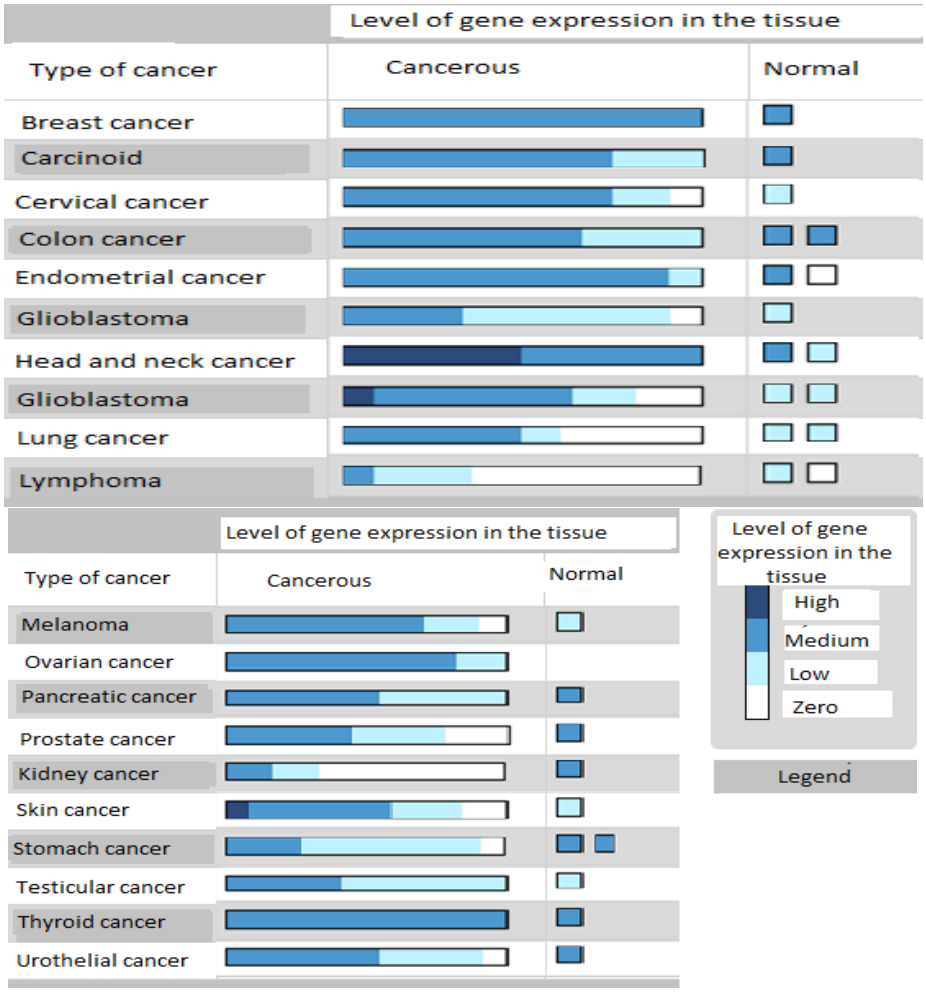


Figure. 6 FGFR1 gene expression in healthy tissue and tumor altered based on (64).

List of abbreviations

3T3-L1 – line of mouse fat cells
αKL – gene α Klotho
cDNA -*complementary DNA*
CYP1A1 - cytochrome P- 450 1A1
DEPC -*Diethylpyrocarbonate*
ER – α *Estrogen receptor alpha*
ER- β *Estrogen receptor beta*
FGF -*fibroblast growth factor*
FGFR -*fibroblast growth factor receptor*
FIGO -*fr. Fédération Internationale de Gynécologie et d'Obstétrique*
G1, G2, G3 - *grading*
HCC - *hepatocellular carcinoma*
HBS -*heparan sulfate binding site*
HPRT1 -*hypoxanthine-guanine phosphoribosyltransferase*
HS - *heparan sulfate*
IGF – 1 -*insulin-like growth factor 1*
KRAS -*Kirsten rat sarcoma viral oncogene*
KLB – βKlotho gene
KLPH - KL lactase phlorizin hydrolase
LCTL -lactase-like protein
MTHFR- *methylenetetrahydrofolate reductase*
PR A -*progesterone receptor*
PR B -*progesterone receptor*
PTEN -*phosphatase and tensin homolog*
SHGB -*sex hormone binding globulin*
SERM -*selective estrogen receptor modulator*

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