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# Molecular Biology of Endometrial Carcinoma

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## 1. Introduction

The term tumour is understood as a general denomination for newly formed tissue formation or cell populations in an organism that do not develop as a physiological response to external or internal stimuli, show abnormality signs and more or less escape the regulatory influence of the surrounding cells and organism. Currently, a general opinion has been accepted that tumours result from congenital or acquired genetic damage. Thus, the spectrum of formerly suggested theories of carcinogenesis has narrowed down to a single genetic theory. It is therefore necessary to emphasize that regardless of malignant growth being sporadic for the individual or recurrent for many family members as a hereditary trait, it is clearly a genetic disease.

## 2. Molecular principles of tumour genesis

The process of tumour development consists of several stages and is determined by the imbalance between the cell proliferation and cell death. The cells proliferate if they undergo a cell cycle and mitosis, whereas the destruction, due to a programmed cell death, removes cells from tissues through a standard DNA fragmentation process and cell suicide called apoptosis. These processes of cell division and cell death are regulated by a number of genes. According to the extensive research of several recent decades it is the mutation in genes controlling the cell proliferation and death that is responsible for cancer.

In most malignant tumours mutations appear in a single somatic cell in which, during subsequent division, genetic errors are cumulated, i.e. multistep carcinogenesis. More rarely, if the malignancy occurs under the hereditary syndrome with tendency towards malignant tumours, the initial mutations causing cancer are inherited in the germinal line and are therefore present in every cell in a body. Different types of genes participate in the initiation of the tumorous process, e.g. genes coding proteins of signal pathways for cell proliferation, cell cycle regulators or proteins responsible for detecting and correcting mutations. As soon as the malignant growth is triggered by any mechanism, it develops as accumulation of other genetic changes through mutations of genes coding the cell apparatus that repairs damaged DNA and maintains cytogenetic stability. The damage to these genes results in further impairment in cascaded mutations of the increased number of genes controlling cell proliferation and repairing damaged DNA. The original clone of neoplastic

cells may, in this way, develop into many sublines with a different degree of malignancy. Thus, the cell clone able to survive is selected, i.e. clonal selection. Such tumorous cells generally acquire the ability of invasive growth and metastases.

Each malignant tumour is a mixture of cells with various characteristics as, during the excessive and mostly chaotic and imprecise division, other changes are cumulated and new characteristics acquired. Therefore, the metastatic cells do not reveal different genetic changes than the cells of the original tumour. However, all these cells emerged through the division of a single originally maligned cell and thus the tumour is termed as monoclonal.

The above indicates that the complex tumorous process involves a great number of genes. The main events starting from the carcinogenesis initiation stage to propagation and metastases include activation of proto-oncogenes, inactivation of tumour suppressor genes, microsatellite instability, aneuploidy and loss of heterozygosity (Kolář et al., 2003, Nussbaum et al., 2004).

### 3. Molecular biology of endometrial carcinoma prognostic factors

As already mentioned above, the tumour development is a multistage process. It embraces genetic changes, i.e. direct changes in DNA nucleotide sequence, epigenetic changes not altering the genetic code but affecting its expression (methylation of certain DNA bases or histone acetylation) and functional changes at the cell metabolism regulation or at the level of gene expression control and cell division. Considering genetic changes there are two most significant types of genes: proto-oncogenes and tumour suppressors.

#### 3.1 Oncogenes

The foundations of the theory on existence of genes that may cause tumours (oncogenes) were laid in 1911 when Rous described a transmissible sarcoma in chickens. It was discovered that the transmissible etiologic agent of this tumour was a virus, denominated as Rous sarcoma virus (RSV). In broad terms, the oncogenes are all active genes able to cause or boost up tumorous transformation. There are two forms of oncogenes: viral-oncogene that forms a part of the retrovirus genomes causing tumours and cellular oncogene that develops by activation of the proto-oncogene. Proto-oncogenes are genes of standard eucaryotic cells coding proteins that are important for growth or differentiation of cells. They become potential oncogenes if, due to quantitative changes or qualitative changes in the structure of the actual gene or its protein product with a subsequent defect of a functional interaction with other genes, they are subject to an incorrect expression. The mechanisms of this incorrect expression vary:

- a. point mutation when one or few nucleotides are deleted (deletion) or are, on the contrary, inserted (insertion, duplication) or substituted without a change in the number of nucleotides (substitution),
- b. gene amplification,
- c. gene deletion (loss of large sections of genes),
- d. translocation of chromosomes when an entire chromosome is broken at a specific place and then it is connected to a different chromosome (typical for haematological malignities),
- e. insertional mutagenesis when proto-oncogenes are activated through the insertion of retroviral promoters and enhancers (sequences determining the quantity of the respective gene to be generated, i.e. the quantity of protein produced).

As a consequence, the changes described above may result in an unregulated function or increased expression of the oncogene product and eventually to the stimulation of tumour growth. Under standard conditions, the oncogene products function as growth factors (int-1), hormones and receptors for growth factors and hormones (c-erbB-2), as well as proteins functioning as signal transducers (K-ras) and proteins binding DNA sequences to gene expression regulators, i.e. transcription regulatory factors (c-myc). A specific group includes oncogenes that inactivate tumour suppressor genes (E6 a E7) or inhibit the physiological process of cell renewal – apoptosis (bcl-2).

At the cell level, oncogenes play a dominant role, which means that under activation or increased expression one mutated copy (allele) is able to alter the cell phenotype from normal to malignant (Kolář et al., 2003, Nussbaum et al., 2004, Ruddon, 2007).

Despite a large number of oncogenes known to be related to various malignancies, only certain ones are significant in endometrial carcinogenesis, e.g. bcl-2, c-erbB-2, K-ras, etc.

### 3.1.1 c-erbB-2

The c-erbB-2 oncogene (human cellular oncogene) is identical to HER2/neu (rat cellular oncogene). It codes a transmembrane glycoprotein receptor for a growth factor similar to EGRF (epidermal growth factor receptor). The difference is that the coding gene is located on chromosome 17q21-22 (EGRF on chromosome 7) and that the mRNA size of this gene is only 4.6 kb (for EGRF 5.8 - 10 kb). Under normal circumstances c-erbB-2 protein forms a part of signal transduction pathways and therefore regulates the cell growth, survival, adhesion, migration and differentiation, i.e. functions that are either intensified or, on the contrary, weakened in tumour cells.

In a number of tumours the increased expression of this oncogene is associated with poor prognosis. Its relationship is probably best understood in association with breast carcinoma when its amplification and increased expression occurs approximately in 15 to 20% of cases. The increased expression of this receptor in breast cancer is definitely related to the increased risk of recurrence and poorer prognosis (Kakar et al., 2000). From the clinical perspective, c-erbB-2 protein has been recently found important thanks to its ability to bind monoclonal antibody trastuzumab (Herceptin). Trastuzumab binds solely to the defective protein, i.e. only if the expression of the c-erbB-2 gene receptor has increased. Bound to the tumour cell it also functions as a "lighthouse" identifying the cell. Identified tumour cells are then attacked and killed by their own immunity cells. This prevents further uncontrolled growth of breast carcinoma tumour cells and thus increases the chances of survival (Adam et al., 2008). Recent studies have shown a better effect of trastuzumab in late-stage breast carcinoma. The effect in early stages remains controversial. Other problems lie in the usual development of the resistance of tumour cells to this antibody and last, but not least, its high price (Hudis, 2007). Trastuzumab has also been tested on other tumours with a demonstrated increased expression of c-erbB-2 gene, for instance, on serous papillary endometrial carcinoma (Santin et al., 2008). This preparation has been approved in a number of countries as a first-line therapy for primarily metastatic breast carcinoma - in the Czech Republic since 1 July 2001.

An increased expression of c-erbB-2 also occurs in different tumours, such as ovarian cancer, stomach cancer and endometrial carcinoma. In endometrial carcinomas an increased expression occurs in 10 to 40% of cases and is associated with negative prognostic factors, such as advanced stage of disease and lower degree of histological differentiation (Mariani et al., 2003). It is highly probable that the increased expression of this oncogene might be

among the late events in the endometrial carcinoma carcinogenesis, whereas in serous carcinoma it concerns an early event developed de novo (Matias-Guiu et al., 2001). A negative prognostic impact of a c-erbB-2 expression has been documented in some, but not in all, trials and thus the clinical application of changes in expression of this factor remain ambiguous (Ferrandina et al., 2005, Morrison et al., 2006). The dissimilar outcomes of the respective studies may, to a great degree, be the result of so far non-uniform diagnostic procedures applying either the immunohistochemical methodology or FISH methodology or alternatively CISH methodology.

### 3.1.2 bcl-2

Proteins of the bcl-2 family belong among the significant regulators of apoptosis (for more see Chapter p53). The bcl-2 protein was discovered while studying the chromosomal translocations t(14,18) frequent in some lymphomas resulting in an increased expression of the bcl-2 gene and resistance to apoptosis. The bcl-2 protein family consists of both inhibitors and promoters of programmed cell death. At least 25 members of this family have been identified in mammals, whereas bcl-2 is the typical and best described representative of antiapoptotic proteins and in proapoptotic it is Bax. Many theories based on the experimental results have tried to explain the manner in which the proteins in this family regulate cell death. Originally, it was assumed that bcl-2 functions as an antioxidant transporting proteins through nucleus membrane. It has been recently discovered that it also regulates the activation of caspase-related proteases that are responsible for the final effector stage of apoptosis. Its other functions include the protection of cells against various cytotoxic effects, including various types of radiation and chemotherapy. The bcl-2 family proteins also belong among the important agents affecting chemosensitivity or chemoresistance. Thanks to their ability to block cell death induced by the anti-tumorous drugs bcl-2 may be considered as an important protein active in the development of multi-drug resistance (Wang, 2001).

The antiapoptotic factor bcl-2 derives its name from B-cell lymphoma 2; the respective gene lies on chromosome 18q21.3. This oncogene is not associated with cell proliferation but with cell death. By regulating the cell death, inhibiting apoptosis, it prolongs cell survival and thus contributes to the spread of tumorous process. Numerous studies have demonstrated its role in the oncogenous process of, for instance, melanoma, breast, prostate and lung carcinomas, and it also plays an important role in autoimmunity disorders and schizophrenia (Glantz et al., 2006, Li et al., 2006).

While studying the function of this gene in endometrial tissue, it was demonstrated that the immunohistochemical expression of bcl-2 typically changes during the menstrual cycle. During the proliferation stage of the cycle the expression is high and then during the secretion stage and menstruation it dramatically drops which proves that a bcl-2 expression is controlled by the regulatory mechanisms of sex hormones. It was further demonstrated that the bcl-2 expression grows in endometrial dysplasia, whereas it decreases in endometrial carcinoma. It is therefore probable that the increased expression of this oncogene may be one of the frequent events in endometrial carcinogenesis (Chen et al., 1999). Frequent studies demonstrate the loss of the bcl-2 expression correlates with poor prognosis, deeper invasion, advanced clinical stage and aggressive histological types (Erdem et al., 2003, Ohkouchi et al., 2002). The inversion relationship between the loss of expression and biological aggressiveness of the tumour seems to be an obvious paradox. The mechanisms of this down-regulation have not been exactly described yet. It seems that

based on some experimental studies the bcl-2 expression is at least partially regulated by oestrogens and the tumour suppressor gene p53. For example, Popescu et al. discovered that in colorectal carcinomas the relationship of inverted correlation between bcl-2 and p53 is probably derived from the active bcl-2 down-regulation depending on other genes taking over the antiapoptotic function (Popescu et al., 1998). The antiapoptotic function of bcl-2 seems reduced depending on the alterations of other genes, including p53, which are normally involved in the regulatory mechanism of programmed cell death. Less differentiated and clinically more advanced endometrial carcinomas are often associated with the loss of oestrogen receptors and, on the contrary, an increased expression of the p53 gene, which may, to a certain point, explain the loss of the bcl-2 expression in these tumours. The bcl-2 expression, depending on steroid receptors, could facilitate the identification of high-risk tumours (Markova et al., 2010, Ohkouchi et al., 2002).

### 3.1.3 K-ras

The ras oncogene family embraces more than 100 members with various degree of homology of their effector region. There are 3 main groups of ras genes - K-ras, H-ras and N-ras and they belong among the group of oncogenes coding signal transducers. The K-ras oncogene is located on chromosome 12p12 and codes protein of molecular weight equal to 21 kD, forming a part of a signal transduction pathway modulating the cell proliferation and differentiation. Mutations of this oncogene result in the constitutional activation of this signal pathway with subsequent unregulated proliferation and reduced differentiating ability. Point mutations in codons 12 and 13 are found in about 10 to 40% of endometrial carcinomas and in approximately 16% of endometrial dysplasia cases (Cristofano & Ellenson, 2007). It may be concluded that a similar percentage of mutations of this oncogene in endometrial precancerous and malignant lesions mean that the activation of the K-ras gene is one of the early events in endometrial carcinogenesis. It seems that the K-ras gene mutations are more frequent in well differentiated carcinomas than in papillary serous and clear-cell carcinomas. However, in the majority of cases the mutations of the ras gene do not correlate with staging, grading and depth of myometrial invasion and therefore the significance of this marker in prognosis is so far controversial (Lagarda et. al, 2001).

### 3.1.4 C-myc

It belongs among nuclear proto-oncogenes and is the precursor for protein associated with nuclear chromatin. The C-myc gene is located on chromosome 8 and its product functions as a transcription factor. If stimulated by growth factors its expression increases ten to twenty times and it may be an important regulator of cell growth and oestrogen-induced differentiation. The c-myc levels are significantly higher in endometrium than in any other tissue compartments of the uterus. Recent studies have demonstrated an increased c-myc expression in 3 to 19% of endometrial carcinomas (type I) and the immunohistochemical staining for c-myc represented an independent prognostic factor (Geisler et.al., 2004).

## 3.2 Tumour suppressor genes

Genes contributing to malignancy in a completely different manner than oncogenes, i.e. through a loss of function in both alleles of a certain gene, are identified as tumour suppressor genes. They regulate cell division or are involved in contact inhibition of cell growth - they function as "safety fuses" which turn off the cell cycle if exposed to

abnormal proliferation or damage to genetic information. Their protein products check the correctness and preciseness of division and are able to either correct the errors, "care takers", or prevent the cell from going to the next division stage, "gatekeepers". Other products are able to induce even cell death, apoptosis (e.g. p53). Any damage to these genes results in malignant growth as the cell escapes the control mechanisms, which allows for accumulation of secondary mutations of either proto-oncogenes or other tumour suppressor genes leading to a superiority of factors supporting growth, invasiveness and development of a tumour.

The types of tumour suppressor gene disorders are similar to those typical for oncogenes, such as point mutation, amplification, deletion, etc. A full gene or a larger section of a chromosome may get lost in tumour suppressor genes. This loss is manifested as so called loss of heterozygosity (LOH), see below.

While in oncogenes the tumour process may be initiated by damage to just one copy, the genes coding for the tumour suppressors are recessive, which means that the tumour suppressor gene is inactivated only if both its alleles are affected. Inactivation of just one allele is usually insufficient. This Knudson's two-hit hypothesis was applied for the first time to explain how tumours such as retinoblastoma occur in both hereditary as well as sporadic form (Knudson, 1971). In hereditary tumours the cells heterozygous for mutation include another functional copy of a tumour suppressor gene that is sufficient to maintain the normal cell phenotype. However, a cell that accidentally loses the function of the second, remaining, allele loses its ability to suppress the development of a tumour. This "second hit" most frequently concerns a somatic mutation and thus tumours in hereditary syndromes frequently develop repeatedly in the same tissue. On the other hand, in sporadic forms of malignancies resulting from a loss of the tumour suppressor gene only a single cell is probably affected by such a rare event, which means two hits in one cell. These tumours are usually monoclonal and the original tumour occurs in one place which may, however, subsequently widely metastasize. At present, the two-hit model is widely recognized as a basis for hereditary as well as sporadic malignant tumours caused by mutations making the cell lose the function of both copies of a tumour suppressor gene (Kolář et al., 2003, Nussbaum et al., 2004, Ruddon, 2007).

In endometrial carcinogenesis, mutations of various tumour suppressor genes have been shown, such as p53, PTEN, p16, p21, MLH1, MSH2, MSH6.

### 3.2.1 p53

The defects of this gene located on chromosome 17p13.1 belong among the most frequent in human tumours. It mostly concerns mutations of both alleles of somatic cells but hereditary mutations of one allele have been described as well, which significantly increases the risk of the second allele mutation and subsequent development of a tumour. Members of families suffering from one allele mutations of the p53 gene are faced, based on epidemiological studies, with a 25 times higher occurrence of malignant tumours than other population (i.e. Li-Fraumeni syndrome).

The p53 gene codes for nuclear phosphoprotein bound to specific DNA sequences. The product of the p53 gene works as a transcription factor and in cells it takes the form of tetramer that, under normal conditions, stimulates an expression of various genes and thus plays an important role in the cell cycle and apoptosis. The expression of a normal, unmutated, so called wild-type p53 protein increases as a physiological response to

various stimuli inducing cell stress. This results in holding the cell cycle in G1-S regulation point and during this resting period various cell analyzers assess the degree of DNA damage. If the defect is repairable p53 initiates the repair process of damaged DNA sequences; if the defects are rather serious p53 launches mechanisms of apoptosis. This control system is very important in preventing the transmission of defective genetic information to daughter cells. Therefore, p53 is sometimes described as "the guardian of the genome" (Kolář et al., 2003).

Apoptosis is a genetically determined mechanism irreversibly removing damaged cells from most types of tissues. It concerns a programmed cell death and it plays a focal role in tissue homeostasis. During apoptosis the important interlink p53 ensures an expression of specific genes, such as Bax, GADD45 and p21, which activate endonucleases. These enzymes then, under presence of Ca and Mg, degrade DNA to numerous oligonucleosomal fragments and cause disintegration of cell nucleus and destruction of the cell. Subsequently, the apoptotic residues are absorbed by the surrounding cells and degraded in lysosomes. The paradox is that despite p53 activating a large number of genes none of them are able to self-induce the cell apoptosis. Not even p53 is able, on its own, to determine the future destiny of a cell after DNA damage. In addition to factors inducing apoptosis the important products, on the contrary, selectively stimulate proliferation and thus inhibit the apoptosis. Such inhibitors include various growth factors, sex hormones and oncogene products. In this respect the most thoroughly studied is the effect of the bcl-2 oncogene (antiapoptotic gene), product of which concerns the bcl-2 protein (see chapter Bcl-2). Its abundance inhibits the destruction of a cell through apoptosis and supports cell proliferation. In tumours, apoptosis occurs spontaneously and its progress depends on the type of tumour. Considering it plays a crucial role in tissue homeostasis it is understandable that a great deal of attention has been paid to apoptosis (Wang et al., 2001).

The presence of a mutated p53 gene is conventionally proved by immunohistochemical staining. The life span of a wild-type, unmutated product of the p53 gene is short and therefore it is basically undetectable by the immunohistochemical staining. The gene damage caused by various types of mutations results in an increased expression of the mutated p53 protein with an altered function and it is therefore functionally defective and resistant to degradation. Its prolonged biological half-time allows for immunohistochemical detection of the p53 protein product (Battifora et al., 1994). It has been demonstrated that the increased expression of the mutated p53 protein and related strong immunohistochemical staining is primarily a result of so called "missense" mutations (substitution of a single nucleotide or point mutation in a DNA sequence may alter the coding triplet and cause the replacement of an amino acid in the gene product for a different one - therefore such mutations are called mutations changing the codon sense, "missense mutations", because they alter the sense of the codon by specifying a different amino acid . Another type of mutations concerns so called "nonsense mutations" resulting in the occurrence of a shortened protein). Alterations of p53 caused by the substitution of bases, deletion or insertion have been shown in approximately 20% of endometrial carcinomas. In general, p53 mutations are more frequent in poorly differentiated adenocarcinomas; papillary serous carcinomas demonstrate increased expression in up to 80% (Tashiro et al., 1997). Frequent studies demonstrate the correlation between an abnormally increased expression of p53 and aggressive histological types, advanced stage

of disease and shorter survival time (Cherchi et al., 2001, Marková et al., 2010, Ohkouchi et al., 2002). It seems that the p53 gene mutations play an important role primarily in the late stages of endometrial carcinogenesis.

### 3.2.2 PTEN

The PTEN tumour suppressor gene means Phosphatase and TENsin homolog. Alternatively, it is sometimes identified as MMAC1 (Mutated in Multiple Advanced Cancer). The gene is located on chromosome 10q23.3 and codes for protein of molecular weight 47 kD that works as a tumour suppressor. It regulates the interaction between the cell and intracellular matrix that are closely connected with apoptosis. For its correct function the co-operation with p53 and Rb signal pathways is necessary.

The PTEN gene protein demonstrates lipid phosphatase and protein phosphatase activity. Under the lipid phosphatase activity it negatively regulates the level of phosphatidylinositol (3,4,5)-trisphosphate and is able, partially in co-operation with the increased regulation of cyclin-dependent kinase inhibitor p27, to block the cell cycle in the G1/S stage. The protein phosphatase activity includes the regulation of functions of the main adhesion and signal receptor proteins, which mediate the cell migration and invasion, and also controls cytoskeletal organization, cell growth and apoptosis. Therefore, the combination of defects in both functions (lipid and protein phosphatase) may result in defective cell growth and possible escape from apoptosis as well as in possible abnormal cell spread and migration (Wu et al., 2003).

The PTEN gene mutations have been found in various types of human tumours. In germ cells these mutations are found in autosomal dominant Cowden syndrome defined by the occurrence of numerous hamartomas and the increased risk of breast and thyroid cancer. Somatic mutations have been identified in various types of malignant tumours, such as brain glioblastoma, skin melanoblastoma, breast or prostate carcinoma (Li et al., 1997). At present, the PTEN gene mutation is considered to be the most frequent gene alteration in endometrioid carcinoma. In sporadic endometrial carcinoma the mutations of this gene have been described in 30 to 50% of cases while the loss of heterozygosity of chromosome 10q23 occurs in about 40%. Considering that up to 55% of precancerous lesions of endometrial carcinoma show some alteration of the PTEN gene, the lost function of this gene may belong among the early stages in endometrial carcinogenesis (Mutter & Lin, 2000). In non-endometrioid types of carcinomas the PTEN gene mutations are, on the contrary, extremely rare. The responsible genetic alterations, if the expression and function of PTEN are lost, thus usually concern mutations; the loss of heterozygosity without mutation is less frequent. In approximately 20% of cases the cause for loss of expression has been determined to be methylation of promoter, out of which the majority concerns the clinically worse stages of endometrial carcinoma. The inactivation of the PTEN gene caused by mutation correlates with the early stage of disease and better survival. A five-year survival period in cases demonstrating PTEN mutations is found in about 80% of patients compared to a 50% survival chance in cases without mutation. Some authors have described the relationship between the microsatellite instability (MSI) (see below) and PTEN gene mutations. In approximately 50% of cases of endometrial carcinomas with positive MSI the PTEN gene mutations have been detected as short coding mononucleotide repeats resulting in a frameshift mutation. Therefore, the deficit in the mismatch repair system (see below) that represents the final step in acquiring the MSI phenotype may result in frameshift mutation

of the PTEN gene and thus may represent the earliest step of the multistep progression of endometrial carcinogenesis. It seems that the detection of the altered PTEN gene expression could be used as a diagnostic marker of precancerous endometrial lesions (Mutter & Lin, 2000).

### 3.2.3 p21

The p21 is a tumour suppressor gene coding for p21 protein also known as CDKN1A (cyclin-dependent kinase inhibitor 1A) and is located on chromosome 6p21.2. The product of this gene takes an active part in a very complex process of cell cycle regulation. The p21 gene expression is strictly controlled by the p53 tumour suppressor gene which, through transcription activation of the p21 gene followed by an inhibition of cyclin-dependent kinases, stops the cycle in the G1 stage and prevents it from entering the S stage. Furthermore, the p21 protein co-operates with PCNA (proliferating cell nuclear antigen), inhibits the activity of a complex of CDK2 and CDK4 cyclins and thus plays the regulator role during the DNA replication in the S cycle stage. This gene thus represents, especially in co-operation with p53, an important factor in the process of cell growth control and its inactivation may potentially lead to tumorous spread (Gartel et al., 2005). It has also been demonstrated that the p21 expression may be reduced even without the direct effect of the p53 gene, which would be that the inactivation of the p21 gene may also include other mechanisms.

Compared to a normal endometrial tissue, the reduced expression of p21 has been described in the endometrial carcinoma. An univariate analysis of certain studies has shown that the loss of the p21 expression correlated with a shorter survival, however, a multivariate analysis has not demonstrated any prognostic impact (Salvesen et al., 1999).

### 3.2.4 p16

The p16 is a tumour suppressor gene coding for p16 protein also known as CDKN2A (cyclin-dependent kinase inhibitor 2A) and is located on chromosome 9p21.3. It also plays an important role in the regulation of the cell cycle and the p16 gene mutations increase the risk of developing numerous malignant diseases, in particular melanoma. The protein product of the p16 gene is able to bind itself to cyclin-dependent kinase CDK4 and inhibit catalytic activity of the CDK4-cyclin D complex which negatively affects the cell cycle.

In addition to melanoma, p16 gene mutations are also associated with an increased risk of developing other types of malignancies, such as carcinoma of the pancreas, stomach or oesophagus. In endometrial carcinomas the p16 gene alterations occur more rarely. However, the loss of the p16 protein expression has been identified in association with aggressive types of endometrial carcinomas, plus in connection with high proliferation activity of the Ki-67 marker. It seems that the degree of the p16 nuclear expression may be used as an independent prognostic factor in endometrial carcinomas (Salvesen et al., 2000).

### 3.2.5 Mismatch repair system genes

Under the hereditary breast and ovarian carcinoma syndrome it is also definitely necessary to include so called mismatch repair system genes MMR (MLH1, MSH2, MSH6, PMS1 and PMS2 ) among the tumour suppressor genes. The vast majority of patients

carry so called Lynch syndrome, also known as HNPCC (hereditary nonpolyposis colorectal cancer). HNPCC is a familial cancer syndrome caused by mutations in one of five different genes for DNA repair responsible for the repair of DNA segments in which the correct pairing of bases has been disrupted - so called mismatch repair system genes. Genes for HNPCC are the prototype of tumour suppressor genes of the "caretaker" type. The probability of germline mutation of mismatch repair system genes being transmitted from parents to children is 50%, thus it is an autosomal dominant mode of inheritance. Same as for other tumour suppressor genes the autosomal dominant mode of inheritance is derived from the inheritance of one mutated allele and subsequent mutation or inactivation of the remaining normal allele in a somatic cell. At the cell level, the most apparent phenotypic manifestation concerns the enormous increase in point mutation and instability of DNA sequences containing simple repeats (see chapter Microsatellite instability). This instability known as "replication error positive" phenotype appears in cells that lack both copies of the gene for DNA mismatch with a frequency one hundred times higher (Lu & Broaddus, 2005, Nussbaum et al., 2004).

The lifelong risk of developing endometrial carcinoma is between 27 and 71% and the risk of colorectal carcinoma between 24 and 52%. The above risks depend on the gene in which the respective hereditary defect is localised; the crucial role in carcinogenesis of endometrial carcinoma is probably played by the inactivation of the MSH2/MSH6 complex. In terms of other possible malignancies, there is an increased risk of ovarian carcinoma (3-13%). HNPCC is also associated with an increased risk of stomach cancer (2-13 %), urinary tract cancer (1-12%), hepatobiliary tract cancer (2%) and brain tumours (1-4%). Carcinoma of the small intestine is considered to be a very sensitive indicator of hereditary disposition as it is very rare in the general population (the lifelong risk for an individual with disposition is 4 to 7%, which is 25 to 100 times higher compared to the general population) (Vasen et al., 2007). The risk of breast cancer may be slightly increased.

In patients with HNPCC the endometrioid carcinoma is to a certain point similar to the type I carcinoma as in the vast majority of cases it is diagnosed in stage I (78%), occurs earlier in life (median age is 40 years), shows endometrioid histology (92%) and often a higher grading. Under the Lynch syndrome tumour duplicity with colorectal carcinoma is very frequent (up to 61%) while in about 50% of these patients the first diagnosis is gynaecological. In molecular analysis of tumours, in addition to microsatellite instability, mutations and inactivation of the PTEN tumour suppressor gene are found (in up to 90% of cases). In terms of prognosis, endometrial carcinomas in women with MMR system gene mutations are not different from the same-stage tumours in women without the hereditary mutation (Zhou et al., 2002).

### **3.3 Microsatellite instability**

Under the organization of the human genome structure we differentiate between the DNA coding sequences, which take up less than 1.5% of the genome, and noncoding sequences, which take up the remaining 98.5% of the total DNA. About one half of this noncoding DNA consists of various types of repetitive sequences, i.e. DNA sections of various length that appear in many copies at various places of the genome. Most of them are products of reverse transcription and thus they have a crucial effect on the structure of the genome in

humans and other organisms. The importance of the repetitive sequences probably lies in maintaining the chromosomal structure and apparently they also play an important role in the evolution of genes and genomes (Venter et al., 2001).

Microsatellite DNA refers to sections with repeats of 2 to 5 nucleotides occurring in various places of the genome. They are highly polymorphous and, simultaneously, they represent the most frequent form of repetitive DNA. They are specific for each individual, which provides a basis for precise identification used in forensic medicine. Thanks to its repetitive structure the microsatellites are susceptible to errors in replication. Mutations in these short sequences, known as microsatellite instability (MSI), are usually repaired by a protein system of various genes that are able to replace the incorrect bases in DNA. The most well-known include MLH1, MSH2 or MSH6, which are genes of the mismatch repair system (MMR). These genes may be inactivated by various mechanisms, in particular by mutation or methylation. MSI occurs in up to 90% of hereditary colorectal carcinoma but it has also been detected in sporadic tumours (Lynch et al., 1996). The majority of sporadic endometrial carcinomas do not show mutations in MMR genes; the likely cause of MSI in this type of tumour concerns hypermethylation of the MLH1 promoter resulting in epigenetic inactivation of the MLH1 gene. MSI has been found in about 30% of endometrial carcinomas, especially in endometrioid types I, and is associated with a favourable prognosis. Although the majority of studies have not demonstrated the correlation between MSI and age, grading, clinical stage and depth of myometrial invasion, a five-year survival in patients with endometrial carcinoma with positive MSI was by about 20% better than in patients without MSI. On top of that the endometrial carcinomas with MSI more frequently show mutations in the PTEN gene and a less frequently increased expression of p53, which is a typical abnormality for nonendometrioid types of tumours (Maxwell et al., 2001).

### **3.4 Loss of heterozygosity (LOH)**

Each chromosome carries a different set of genes linearly placed in chromosomal DNA. Homologous chromosomes carry paired genetic information, i.e. the same genes in the same sequence. In any specific locus, however, there may be two identical or slightly different forms of the same gene, i.e. every gene in our chromosomes is present in two forms, called alleles (one chromosome of each chromosomal pair is inherited from the father, the other from the mother). If one parental allele is lost, an effect called hemizyosity occurs. When analysing a tumour such a gene deficit is manifested as a loss of heterozygosity - LOH. In human solid tumours this loss of heterozygosity also usually means the loss of the tumour suppressor gene. LOH thus represents, according to the two-hit theory, the second hit to the remaining normal allele. It may result from interstitial deletion, somatic recombination or loss of the entire chromosome.

LOH has been described in many tumours, hereditary as well as sporadic (e.g. retinoblastoma, breast or colorectal carcinoma) and it is often considered to be the evidence of the tumour suppressor gene existence despite the gene has not been found yet. The studies of LOH while focusing on specific spots in the genome that could contain tumour suppressor genes associated with endometrial carcinoma have been carried out by several authors. In relation to endometrial carcinoma LOH has thus been demonstrated on many chromosomes, but the locuses on chromosomes 3p, 10q, 17p and 18q seem rather specific.

Numerous losses of heterozygosity are typical for nonendometrioid carcinomas (Albertson et al., 2003, Tashiro et al., 1997).

### **3.5 Aneuploidy**

A certain degree of genetic instability that may, as a result of defects in mitotic segregation or recombination during cell division, lead to significant changes in the genome is typical for the genetic material in tumour cells. Normal somatic cells with 46 chromosomes (23 pairs) are called diploid cells, while extra or missing chromosomes are identified as aneuploidy. Chromosomal instability causing structural or numeric aberrations occurs in early as well as later and more invasive stage of tumour development and is typical for various types of malignant tumours. These cytogenetic changes indicate that defects in genes associated with maintaining chromosomal stability and integrity and assuring the exact mitotic segregation represent a significant element of tumour progression (Nussbaum et al., 2004).

In endometrial carcinoma the aneuploid changes occur in 25 - 30% of cases. According to a number of studies approximately 67% of endometrioid carcinomas are diploid, whereas about 55% of nonendometrioid carcinomas demonstrate aneuploid changes (Mutter & Baak, 2000). Diploid tumours are usually well differentiated tumours with only surface invasion to myometrium and are associated with longer survival than aneuploid tumours. Aneuploid tumours are in general associated with a poorer prognosis, higher number of recurrences and shorter disease free survival. The percentage of disease free survival for tumours in stage I, which is 94%, versus 64% in aneuploid tumours shows a clear difference. The important fact remains that in the vast majority of studies the ploidity is mentioned as independent prognostic factor (Pradhan et al., 2006, Suehiro et al., 2008).

### **3.6 Other prognostic markers**

#### **3.6.1 Ki-67**

One of the most well-known markers of cell proliferation includes the Ki-67 protein, also known as MKI67. The respective gene (MKI67) coding for this protein is located on chromosome 10q25. The expression of the Ki-67 human protein is strictly associated with cell proliferation. During interphase Ki-67 can be easily detected within the cell nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. The Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2 and mitosis), but its expression is basically absent from resting cells (G0). That is the reason why Ki-67 can be identified as an excellent marker to determine the growth fraction of a given cell population. This growth fraction of Ki-67-positive tumour cells (Ki-67 index) is often correlated with clinical stage of various malignant diseases. The best-studied examples in this context are prostatic and breast carcinomas. For these types of tumours the prognostic value for survival and tumour recurrence have repeatedly been proven in uni- and multivariate analyses.

MIB-1 is a commonly used monoclonal antibody that detects the Ki-67 antigen. One of its primary advantages is that it can be used on formalin-fixed paraffin-embedded sections, which is the reason why it has essentially supplanted the original Ki-67 antibody for clinical use. Recently the use of the Ki-67 protein as proliferation markers in laboratory animals has been expended to embrace the preparation of new monoclonal antibodies

prepared from rodents. Although the molecular level of the Ki-67 protein has been well-studied and its application as a proliferation marker is widely used, its functional meaning is still not fully clear. Nevertheless, there is obvious evidence that the Ki-67 protein expression is indispensable for the cell division process to be successful (Scholzen & Gerdes, 2000).

Most endometrial carcinomas demonstrate a low Ki-67 proliferation index with a favourable prognosis, while most serous and clearly cellular tumours demonstrate a high proliferation index with poor prognosis. The correlation with grading, stage of the disease and histopathological type of tumour has been confirmed by many studies (Ferrandina et al., 2005, Markova et al., 2010).

### 3.6.2 $\beta$ -catenin

$\beta$ -catenin is a submembranous protein that is encoded by the CTNNB1 gene located on chromosome 3p21.  $\beta$ -catenin is a part of a complex of proteins that constitute adherens junctions which are necessary for the creation and maintenance of epithelial cell layers by regulating the cell growth and adhesion between cells. Therefore, it takes part in maintaining tissue architecture. It is known that  $\beta$ -catenin is able to bind to various proteins. For example, it creates complexes with cadherines, which are transmembrane proteins functioning as transcription factors, so it plays an important role in regulating transcription. It is also known that it represents an integral component of the Wnt signal pathway, which is a network of proteins with a significant role in embryogenesis and tumorigenesis (Bullions & Levine, 1998).

Under defects of the above functions  $\beta$ -catenin can function as an oncogene. An increased level of  $\beta$ -catenin and mutations of the CTNNB1 gene have been described in various tumours - basal cell carcinoma, colorectal carcinoma, medulloblastoma or ovarian carcinoma. In endometrial carcinoma the nuclear accumulation of  $\beta$ -catenin and, simultaneously, mutations of its CTNNB1 gene have been described in many studies. The nuclear  $\beta$ -catenin has been identified in 16 to 38% of endometrial carcinomas, while its expression was significantly higher in the endometrioid (type I) (31 - 47%) than in nonendometrioid (type II) (0 - 3%) carcinoma. Mutations of CTNNB1 in endometrioid carcinoma have been described in 15 to 25%, while in nonendometrioid carcinoma none has been identified. Accumulation of  $\beta$ -catenin in cell nucleus has been found in less aggressive tumours with low metastasizing potential and, similarly, mutations of CTNNB1 are associated with well differentiated carcinomas (Machin et al., 2002, Scholten et al., 2003).

### 3.6.3 Steroid receptors

Endometrium is the target tissue of steroid hormones produced by ovaries. Oestrogen (ER) and progesterone (PR) receptors are present in both epithelial and stromal endometrial cells. It is generally known that ovarian steroids, oestrogen and progesterone, have the critical importance for regulating the growth and differentiation in endometrial cells. A normal course of the menstrual cycle (proliferation, differentiation and degeneration of endometrium) reflects cyclic changes in sex steroid levels. The proliferation stage of the cycle is mostly under the influence of oestrogens that stimulate proliferation of epithelial and stromal endometrial components, whereas during the secretory stage the main function

of progesterone is glandular differentiation and glycogenesis with inhibition of oestrogen-mediated proliferation. Just as the ovarian steroids play an indispensable role in normal endometrium, they also significantly influence the development of endometrial carcinoma (Graham & Clarke, 1997).

ER and PR belong among a group of nuclear receptors with typically immunohistochemically detectable cyclic changes in their expression based on the cycle stage. After their activation they bind to specific target places in DNA where they modulate an expression of respective genes. In addition to this direct activation of target genes an indirect mechanism of their effect via relation to transcription factors, such as AP-1 (c-fos, c-jun) or NF- $\kappa$ B, has been described (Oehler et al., 2000).

Oestrogen receptors (ER) belong among the group of receptors subject to  $17\beta$ -estradiol activation. ER primarily function as a transcription factor regulating the expression of other genes. Two subtypes of ER, ER $\alpha$  and ER $\beta$ , have recently been described; each of them is encoded by a different gene. The ESR1 gene for ER $\alpha$  is located on chromosome 6q24-q27, the ESR2 gene for ER $\beta$  on chromosome 14q21-q22. ER play an important role in the development of various malignancies, primarily in breast cancer (an increased expression is indicated in about 70% of cases) cancer of the ovaries, colon, prostate and, of course, endometrial carcinoma. While ER $\alpha$  is the dominant receptor in endometrium and participates primarily in increased proliferation, ER $\beta$ 's effect is anti-proliferating and it apparently modulates the ER $\alpha$  function. The imbalance between the expression of ER $\alpha$  and ER $\beta$  is considered to be the critical moment in oestrogen-dependent carcinogenesis (type I). In endometrial carcinoma a decreasing level of the ER $\alpha$  mRNA expression and protein has been described, together with dedifferentiation of this tumour from grade 1 to grade 3. Under the unchanged expression of ER $\beta$  the ER $\alpha$ /ER $\beta$  ratio decreases (Jazaeri et al., 2001). In addition to the changed ratio of ER isoforms, incorrectly transcribed proteins derived from ER $\alpha$  or ER $\beta$  take part in endometrial carcinogenesis. For example, they include 5 ER $\alpha$ , which has been described in endometrial carcinoma but has not been detected in normal endometrium, or ER  $\beta$ cx with a dominant negative effect on ER $\alpha$  (Skrzypczak et al., 2004).

The progesterone receptor (PR), also known as NR3C3 (nuclear receptor subfamily 3, group C, member 3), is an intracellular receptor able to specifically bind progesterone.

PR is encoded by one PGR gene located on chromosome 11q22. It also exists in two isoforms differing by their molecular weight: PR-A and PR-B. One of the main functions of PR-A in endometrium is down-regulation of oestrogen activity via ER $\alpha$  inhibition. On the other hand, PR-B works as an oestrogen agonist in endometrial cells. Imbalances in PR-A/PR-B ratio are similarly considered to be a critical moment in the development of endometrial carcinoma (type I) (Arnett-Mansfield et al. 2001).

A number of studies have demonstrated that the presence and quantity of these steroid receptors correlate with the stage of tumour, grading and survival. The absence of steroid receptors is seen as a negative prognostic factor of aggressive growth and poor prognosis (Ferrandina et al., 2005, Jazaeri et al., 2001, Pilka et al., 2008). Nevertheless, the mechanisms of the loss of their expression in endometrial tumours is not fully known.

#### 3.6.4 Growth factors

Steroid hormones regulate a number of growth factors that apparently participate in the paracrine and autocrine regulation of endometrial proliferation. They primarily include

epidermal growth factor (EGF) and transforming growth factor alpha (TGF-  $\alpha$ ), which influence the endometrial cells through an EGF receptor. Both growth factors and their receptor stimulate cell growth in endometrial carcinoma in vitro. Other growth factors involved in endometrial carcinogenesis (type I) include transforming growth factor beta (TGF-  $\beta$ ), basic fibroblast growth factor (bFGF) and insulin-like growth factor I (IGF-I) (Myeroff et al., 1995).

### 3.6.5 Matrix metalloproteinase

Matrix metalloproteinase belongs among the family of enzymes of zinc-dependent endopeptidases that are capable of degrading extracellular matrix. So far, more than 25 subtypes of these enzymes have been identified; based on their structure they are further classified into 8 different classes and their production is induced by an inflammatory or tumorous process (Nagase et al., 1999). One of the important members of the metalloproteinase family with an epithelial expression concerns MMP-7 (matrilysin-1), expression of which has been detected in both normal and malign epithelial cells. Only a limited number of studies focused on the MMP-7 expression in endometrial carcinoma has been published. In his study Ueno et al. demonstrated an increased expression of MMP-7 correlating with the worse clinical stage of the disease and presence of lymphatic metastases (Ueno et al., 1999). A similar trend is also described in the study carried out by (Graesslin et al. 2006, Wang et al., 2005). Markova et al. describes a significant relation between age and MMP-7 as in patients older than 65 the expression of MMP-7 was significantly lower (Markova et al., 2010).

Another member of the matrilysin enzymes subfamily is identified as MMP-26 (matrilysin-2). Likewise, MMP-26 is also generated in various tissues, both normal and malignant, including endometrial carcinoma. The outcomes of studies carried out by various authors indicate that despite MMP-26 belonging among the same subfamily of metalloproteinases as MMP-7, its function may apparently be different. It is known that the expression of MMP-26 specifically fluctuates during the menstrual cycle. The detection of high levels in the middle of the cycle and in hyperplastic endometrium, and, on the other hand, low levels in the late stage of the cycle and endometrial carcinoma indicate the correlation with oestrogen receptors. Isaka et al. and Pilka et al. demonstrated a significantly reduced expression of MMP-26 in endometrial carcinoma, which goes against the results of study carried out by Tunuguntla et al., who describes an increased immunohistochemical expression of MMP-26 in low-differentiated endometrial carcinoma (Isaka et al., 2003, Pilka et al., 2004, Tunuguntla et al., 2003).

## 4. Conclusion

The efficient treatment of malignancies requires an early and accurate diagnosis enabling to optimize therapy and minimize adverse effects. Early diagnosis of cancer, together with individual "custom-made" therapy, may reduce mortality and improve the prospects and quality of the patient's life. Gynaecological malignant tumours represent a group of diseases where the prognosis depends on subtle genomic, epigenetic and proteomic changes. The application of molecular biology techniques, including analysis of methylation and acetylation, and preteomic techniques have become an important tool not only in basic research but also when determining the appropriate therapy.

The significance of various immunohistochemical parameters for the prognosis in patients suffering from endometrial carcinoma has not been unambiguously determined yet. The aim is, by applying the information acquired based on the expression of tumour biomarkers, to limit the radicalism in surgical and radiation therapy. The future objective is to further classify the subtypes of endometrial carcinoma based on their genetic alterations, in particular those that are significant in terms of prognosis. It is probable that future histological classifications will be based more on a molecular basis. In addition to clinical pathological factors, the molecular biological prognostic factor may improve the characteristics of tumours and provide a more accurate definition of their clinical behaviour. Although these factors will apparently be more important in managing the endometrial carcinoma treatment in the near future, any practical diagnostic and therapeutic application of biological factors will require more detailed studies.

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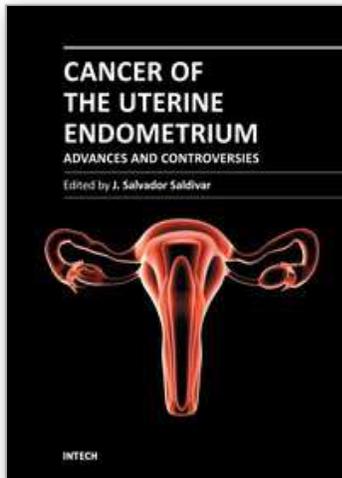
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## **Cancer of the Uterine Endometrium - Advances and Controversies**

Edited by Dr J.S. Saldivar

ISBN 978-953-51-0142-0

Hard cover, 182 pages

**Publisher** InTech

**Published online** 29, February, 2012

**Published in print edition** February, 2012

The book *Cancer of the Uterine Endometrium - Advances and Controversies* brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source of advances in the diagnosis and therapeutic strategies in this field of gynecologic cancer. Each section in the book attempts to provide the most relevant evidence-based information in the biology and genetics, modern imaging, surgery and staging, and therapies for endometrial cancer. It is hoped that future editions will bring additional authors to contribute to this endeavor. To this end, it is our patients who will benefit from this work.

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Ivana Markova and Martin Prochazka (2012). Molecular Biology of Endometrial Carcinoma, *Cancer of the Uterine Endometrium - Advances and Controversies*, Dr J.S. Saldivar (Ed.), ISBN: 978-953-51-0142-0, InTech, Available from: <http://www.intechopen.com/books/cancer-of-the-uterine-endometrium-advances-and-controversies/molecular-biology-of-endometrial-carcinoma>

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