The role of epigenetics in endometrial cancer

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Endometrial adenocarcinoma, often referred as the endometrial cancer, is the most common kind of uterine cancer. It´s incidence is rising in last decades and each year tens of thousands of women worldwide are diagnosed with one of two types of endometrial cancer. It is observed that relatively higher incidence is in the developed world countries, in North America and central Europe. These unfortunate statistics are also an opportunity for these regions to study its forming process and possible ways how this malignancy emerges on the cellular level. As it is with such multifactorial diseases, it undergoes a complex development during which affected cells undergo many changes in their genetic information as well as in their epigenetic modifications. Not all of them should be considered the oncological drivers, but passengers of the rapid changes in adenocarcinoma tissues may also affect its staging. Therefore, the studies of the mutations, DNA epimutations, changes in histone code or micro-RNA molecules and disturbed hormone signalling pathways may be crucial for understanding of carcinogenesis process. The passengers with significant correlation rates, even though they are not crucial for potential therapy, may have their role in the development of new diagnostic tools. In this article, we provide a review of epigenetic changes affecting endometrial cancer types.
Keywords: **Endometrial cancer development, epigenetics, type 2 endometrial cancer, DNA methylation, OncomiRs**

Úloha epigenetiky pri rakovine endometria
Endometriálny adenokarcinóm, uvádzaný často aj ako rakovina endometria, je najčastejším druhom rakoviny maternice. V posledných desaťročiach možno sledovať nárast jeho výskytu a každoročne sú desaťtisíce žien na celom svete diagnostikované jedným z dvoch typov rakoviny endometria. Známe je, že relatívne vyšší výskyt pozorujeme vo vyspelých krajinách sveta, najmä v štátoch Severnej Ameriky a strednej Európy. Táto nepríjemná štatistika je však tiež možnou príležitosťou pre tieto regióny študovať karcinogenézu a možné spôsoby, aké sú príčiny a dôsledky tejto malignity na bunkovej úrovni. Ako to býva pri multifaktoriálnych ochoreniach, postihnuté bunky prechádzajú nielen mnohými zmenami genetickej informácie, ale aj epigenetickými modifikáciami. Nie všetky by sa mali považovať za kritické pre onkologický proces, no aj sprievodné modifikácie v tkanivách adenokarcinómu môžu ovplyvniť vývoj malignity. Preto môže byť štúdium mutácií, epigenetických zmien v DNA, zmien v histónovom kóde alebo molekulách mikroRNA, prípadne narušených hormonálnych signálnych dráhach kľúčové pre pochopenie procesu karcinogenézy. Sprievodné zmeny s významnou mierou korelácie, aj keď nie sú rozhodujúce pre potenciálnu terapiu, môžu mať svoju úlohu pri vývoji nových klinicky relevantných nástrojov. V tomto článku podávame prehľad epigenetických zmien ovplyvňujúcich oba typy rakoviny endometria.
Kľúčové slová: **karcinogenéza rakoviny endometria, epigenetika, rakovina endometria 2. typu, DNA metylácia, OncomiRs**

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Introduction

Endometrial cancer (EC) is the second most common gynecologic cancer (after breast cancer) and seventh most common cancer worldwide among females[1,2]. Regions of Central and eastern Europe had the second highest cumulative risk in both incidence (2,48%) and mortality (0,47%) in 2020. In estimated age-standardized incidence rates of all ages, Slovakia is ranked 15th of all countries (**Table 1**)[2].

The full mechanisms of EC development remain unclear but there is growing number of molecules (hormones, proteins and RNAs) reported to have a role in carcinogenic process. Mutations in coding regions of functional molecules same as their regulation is crucial for EC development. In last decades, the research is getting more focused on epigenetic changes, such as hypermethylation, deacetylation of histones or RNA interference[1,3,4]. The epigenetic modifications seems to be more frequent in EC that genetic changes, therefore they could potentially serve as a diagnostic tool[4].

Types of endometrial cancer and their differences

There are two types of EC differing in the body estrogen excess and the rate of spreading. Type 1 is more common (80% of cases), growing slower and linked to excess of estrogen. It occurs mostly among premenopausal and perimenopausal women. Type 2, on the other hand, is faster growing one, without apparent multistage pro-

Table 1. The list of countries with highest rate of endometrial cancer in 2020. Both age-standardized rates cumulative risk were estimated for all ages[28].

Rank	Country	Age-standardized incidence (per 100 000)	Cumulative risk (%)
1.	Poland	26.2	4.57
2.	Lithuania	25.4	4.41
3.	Samoa	24.7	3.42
4.	Belarus	23.6	3.59
5.	Jamaica	22.3	5.43
6.	Ukraine	22.1	3.38
7.	North Macedonia	21.8	3.22
8.	Bahamas	21.8	5.55
9.	United States of America	21.4	3.74
10.	Trinidad and Tobago	20.5	4.19
11.	Barbados	20.4	4.38
12.	Cuba	20.1	3.98
13.	Ireland	20.0	3.80
14.	Russian Federation	19.7	3.26
15.	Slovakia	19.7	3.69
16.	Slovenia	19.6	3.82
17.	Greece	19.2	3.34
18.	Canada	18.6	3.32
19.	Bulgaria	18.3	3.08
20.	Czechia	18.0	3.65
21.	Serbia	17.9	3.04
22.	New Zealand	17.7	3.05
23.	Latvia	17.6	3.10
24.	Croatia	16.8	3.16
25.	United Kingdom	16.7	3.42
26.	Singapore	16.4	2.49
27.	Norway	16.0	3.53
28.	Hungary	15.5	2.96
29.	Estonia	15.4	2.86
30.	Malta	15.2	3.32

cess. It is not linked to excess estrogen in the body, mostly developing among postmenopausal women[5,6]. Typical for type 1 EC is sequence of changes from normal endometrium, through hyperplasia, to precancerous lesion (**Figure 1**). The transition from stage-to-stage is believed to be accompanied with accumulation of mutations in oncogenes, tumor suppressor genes DNA maintenance genes and their regulators[6].

Molecular characterization of endometrioid tumors

One of the latest classifications is subtyping the endometrial tumors based on their molecular DNA background. Even though these molecular subgroups has not been implemented in clinical routine so far, studies confirm their prognostic relevance[7,8].

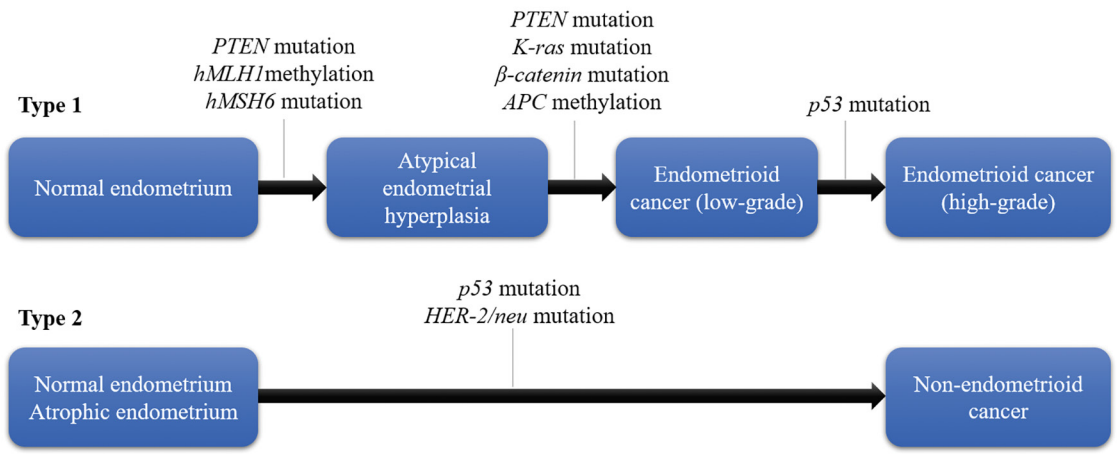
These four groups of carcinomas, independent on histological subtype, are POLE ultramutated (group 1), microsatellite instability (group 2), low-copy-number alterations (group 3), and high-copy-number alterations and *TP53* mutations (group 4)[9,10].

The POLE mutated EC is characterised by pathogenic variants in the DNA polymerase-epsilon (POLE) exonuclease domain mostly in one of the five hot-spots: P286R, V411L, S297F, A456P and S459F. This group presents itself at the younger age of patient and has excellent prognosis[7,10]. The second group is typically mismatch repair (MMR) deficient and the prognostic level is intermediate. The *p53* mutant EC, in accordance with Type 2 classification, presents itself at late stage which corelates with its poor prognosis. The MMR-proficient, POLE and p53 wildtype group, often referred as NSMP EC (no specific molecular profile) has intermediate to excellent prognosis and is associated with higher body mass index[10].

The role of epigenetics - promotor methylation

The regulation of EC stage-to-stage transition could be provided by activity of DNA methyltransferases, particularly *de novo* DNA methyltransferases. Their modification of CpG rich regions (often found in promoter regions, first exons or terminal parts of genes coding untranslated regions) has a crucial role for gene expression. Changed methylation of the *hMLH1* gene is considered one of the earliest steps in multistage endometrial carcinogenesis and is found in ~30 – 40% of cases[11,12]. This gene encodes the homolog of bacterial DNA mismatch repair protein and the malfunctional expres-

Figure 1. Stages of carcinogenesis in both endometrial cancer types[derived from (6) and modified].



sion of the gene (caused by hypermethylation) is associated with other cancer kinds[13-15]. Kawaguchi *et al.*[16] reported that abnormalities in the mismatch repair genes (including *hMLH1*) leads to microsatellite instability which cascades into further mutations and increase in gene instability of other cancer related genes. Therefore, it has been recently proposed, in conformity with the recent group 1 – 4 subtyping, the MMR proteins and loss of MLH1 should be tested for promoter hypermethylation to evaluate its epigenetic mechanism. Subsequent POLE and p53 studies are also encouraged[8].

There is also strong correlation between estrogen levels and expression of *hMLH1*. MMR activity was increased in high estrogen conditions for *in vitro* cultivated endometrial epithelial cells. High estrogen levels could therefore protect from EC development[12]. Cyclic production of estrogen and progesterone in menstruation cycle as well as decline of sex steroid hormone after menopause have direct effect on proliferation and morphology of endometrial tissue[3]. Methylation of the estrogen and progesterone receptor genes were therefore studied in EC cells. They both contain a CpG region in the first exon, but its methylation level have been variable in recent studies, thus its effect is not yet fully understood[3].

During the atypical endometrial hyperplasia, the next stage of EC development, hypermethylation of *APC* promotor is likely to happen, since it is not methylated in normal endometrium, frequently hypermethylated in early cancer stages, but the methylation level is decreasing with an increase in the clinical stage[17]. E-cadherin is tumor suppressor encoded by *CDH1* gene, which promoter is also susceptible to hypermethylation. Decrease of its expression is not only sign of EC development but has an unfortunate 5-year clinical survival rate[18]. Most known affected gene in type 1 EC is *PTEN*. It functions as tumor suppressor gene, regulating proliferation and apoptosis. Its mutation occurs in 26 – 80% of EC, either at development of atypical endometrial hyperplasia or at low grade endometrioid cancer, quite possibly as a consequence of MMR disfunction[3,6]. There is a possibility, that this gene may be downregulated by hypermethylation, as well[19], although, its analysis of the methylation status is quite challenging, since it is 98% identical to *PTEN* pseudogene (psi*PTEN*)[20]. The other methylation affected genes in EC development are regulators of proliferation (*HOXA11*, *TGF-βRII*), apoptosis (*CASP8*), hormone metabolism (*COMT*) or other tumor suppressors (*RSK4*, *P73*, *RASSF1A*). For specifics about their involvement in EC, see[1].

The type 2 EC have distinct methylation patterns. The promotors of many genes mentioned above (*hMLH1*, *APC*, *PTEN*, *RASSF1A*, progesterone receptor coding gene) are detected more frequently in type 1 tumors. Such findings indicates that the process of DNA methylation is predominant in type 1 EC and in type 2 it may have less significant role[3,21,22].

The role of epigenetics - microRNAs

Another way of epigenetic regulation in EC is via microRNA (miRNA) molecules. They may contribute via RNA-associated silencing, but their genes are also under epigenetic regulation. miRNAs are short (19 – 25 nt), noncoding, single-stranded RNA molecules produced by RNA polymerase II or III usually cleaved from primary transcripts by RNase III[4,23]. Targeting of specific miRNA is not trivial since it is potentially able to regulate hundreds of genes and each transcript may be regulated by several miRNAs[24].

The epigenetic regulation of miRNA is occurring on several levels since their production is also regulated by methylation level CpG-rich domains. Favier *et al.*[4] have recently published a complex review for miRNAs with increased (n=140), decreased (n=148) and miRNAs with discordant expression (n=22) in EC from over 100 articles. Additionally, the complex review reports about miRNAs with changed methylation level, six hypomethylated mRNAs and nine hypermethylated ones. Unsurprisingly, the majority of hypermethylated miRNAs (miR-638, miR-137, miR-633, miR-34b, miR-124a-2, miR-124a-3, miR-152, miR-129-2)[4,25-31] are tumor suppressors and the hypomethylated (miR-182, miR-200b, miR-130a/b, miR-625, miR-222, miR-208a)[4,29,32,33] are OncomiRs, the miRNAs associated with the cancer development. Particularly interesting are two miRNAs directly involved in DNA methylation of specific loci. miR-30d is responsible for methylation of CpG region in *H19 noncoding RNA* gene and miR191 downregulates the TET1 expression, the enzyme responsible for methylation removal in promoters of tumor suppressors (*E.g.,* APC)[34,35].

From vast list of miRNAs that are associated with EC and could serve as diagnostic markers, most known are miR-182, miR-183, miR-200 and miR-205[4,36]. miR-182 targets the CUL5 protein, ubiquitin ligase, which has altered expression in several types of cancers. CUL5 overexpression in EC model cell line resulted in decreased cell proliferation[32]. CPEB1 mRNA is targeted, and its expression is downregulated by miR-183, which promotes cell proliferation, migration, invasion, and *in vivo* tumorigenesis in EC[37]. The miR-200 family affects the PI3K/AKT/mTOR by downregulation of PTEN, tumor suppressor protein[4]. Since mR-205 is overexpressed not only in EC[36], but also in other types of cancer[38,39], Favier *et al.*[4] do not find it suitable for diagnosis of EC but considers it as potential prognostic biomarker.

Conclusion

Although, the high number of factors responsible for development of EC, either environmental, hormonal, genetic or epigenetic, we still need many pieces of complex mosaic, to finish the whole picture of this carcinogenic process. Such discoveries might serve as a useful prognostic and diagnostic tool. Because of high rate of EC in regions of Central and Easter Europe (**see Table 1**), we suggest investigating the methylation status Slovak endometrial cancer samples to compare found gene inactivation with known data. Thus, it might be possible to adjust diagnosis in our region.

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