JBUON 2019; 24(6): 2242-2244
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

REVIEW ARTICLE

PTEN mutational landscape in endometrial carcinoma

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Summary

Endometrial carcinoma (EC) represents the most common malignancy of the female genital tract comprising a variety of genomic alterations regarding the two prominent pathological entities: endometrioid and non-endometriod serous mainly carcinomas. Deregulation of significant molecules in signal transduction pathways is a frequent genetic event in their rise and progression. Among them, PTEN (gene locus: 10q23.3-phosphatase and tensin homolog deleted in chromo¬some 10) is a tumor suppressor gene that is deleted, mutated or epigenetically hyper-methylated in a variety of human malignancies. PTEN acts as a negative regulator of this specific pathway. Normal expression of PTEN induces growth suppression by promoting cell cycle arrest. It is also correlated with decreased levels and nuclear local¬ization of cyclin D1 regulated by AKT that positively induces cell cycle. PTEN mutations have been detected in EC cases affecting the biological behavior of the malignancy. In the current molecular review article we explored the role of PTEN deregulation in EC and also in pre-malignant lesions, such as endometrial hyperplasia.

Key words: *PTEN, gene, signaling pathway, endometrial, carcinoma*

Introduction

Endometrial carcinoma (EC) comprises a variety of genomic alterations regarding the two prominent pathological entities: endometrioid (Type I) and non-endometrioid (Type II) carcinomas. Conventional endometrioids are mainly well or intermediate differentiated carcinomas demonstrating a favourable prognosis and increased response rates to specific chemotherapy regimens. In contrast, Type II carcinomas are aggressive malignancies demonstrating pathological patterns of serous carcinomas, clear cell carcinomas, undifferentiated/dedifferentiated carcinomas, and carcinosarcomas [1]. According to the Federation of Gynaecology and Obstetrics (FIGO) revised classification clinicopathologic criteria, EC stage status includes four categories (I-IV) based on their metastatic potential. Conventional endometrioid carcinomas are characterized as FIGO I/II, whereas non-endometrioid are categorized as high grade FIGO III/IV [2]. Extensive genomic analyses have shown that Type I malignancies are characterized by a near diploid karyotype status combined with mutations in suppressor genes and oncogenes including PTEN (gene locus: 10q23.3-phosphatase and tensin homolog deleted in chromo¬some 10), phosphoinositide 3 kinase catalytic subunit α (PI3KCA) and Kirsten ras oncogene homolog (K-RAS, Cytogenetic Location: 12p12.1) [3]. In addition, they demonstrate different molecular patterns of mismatch repair system (MMR) deficiency by detecting mi-

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Received: 17/04/2019; Accepted: 06/05/2019

crosatellite instability (MSI) deregulated markers [4]. In contrast, aggressive Type II malignancies demonstrate significant non-diploid (chromosome polyploidy) levels as gross chromosome instability (CI) combined with p53 (gene location: 17p13.1) suppressor gene and HER-2/NEU (gene location: 17q21) oncogene mutations [5-7]. In the current special molecular article, we explored the role of PTEN deregulation in EC and also in pre-malignant lesions, such as endometrial hyperplasia.

Introducing the PTEN gene and protein

Growth factor receptors (GFR) mediated signal transduction pathways are critical for securing cell proliferation, protein synthesis and survival. Three main GFR dependent pathways have been already identified including the PI3K-AKT-PTEN-mTOR, the RAS-(B) RAF-MEK-ERK/MAPK and also the IL6-JAK1/2-STAT3 [8]. PTEN is a tumor suppressor gene that is deleted, mutated or epigenetically hyper-methylated in malignancies. PTEN acts as a negative regulator of this specific pathway. Normal expression of PTEN induces growth suppression by promoting cell cycle arrest. It is also correlated with decreased levels and nuclear local¬ization of cyclin D1 regulated by AKT that positively induces cell cycle. In fact, downregulation of PTEN is associated with increased PI-3 kinase activity with subsequent higher levels of 3´-phosphorylated phosphoinositides, which bind to and activate Akt [9]. Activated Akt promotes cell survival by phosphorylating and modulating the activity of various transcription factors. Germline PTEN mutations are associated with autosomal dominant hamartomatous and often, cancer-prone syndromes, while homozygous inactivation of the gene has been found in a wide spectrum of sporadic human cancers, including breast and laryngeal squamous cell carcinoma (LSCC) [10,11]. PTEN decreased expression is found to be a negative factor for biological behavior in LSCC patients [12].

PTEN mutations in EC

In fact, the role of PTEN mutations in the development and progression of EC has been well established since the 90s [13]. But in modern molecular era, extensive gene expression analyses based on c DNA microarrays with hierarchical clustering combined with multi-dimensional scaling, and quantitative real time polymerase chain reaction (Q RT-PCR) have detected crucial bio-information regarding PTEN mutational levels in EC cases. A study group focused on analyzing gene expression profiles in Type I and Type II ECs and observed that there are differences regarding a significant number of gene loci, some of them interacting with PTEN [14]. Another molecular study based on targeted sequencing validation by Sanger sequencing, showed that PTEN mutations were prominent in highly aggressive non-endometrioid serous carcinomas followed by other genes such as ARID1A, PIK3CA, and KMT2B [15]. Similarly, another study group analyzed a series of conventional ECs by implementing a combination of PCR high resolution melting analysis (HRMA) and Sanger sequencing in order to detect somatic mutations in PI3KCA (exons 1, 9 and 21) and PTEN (exons 5, 6, 7 and 8), respectively. The authors reported that PTEN mutations affected a significant proportion of the examined cases (67%) [16]. Interestingly, PTEN mutational level in ECs demonstrates differences on the basis of co-existence with MMR deficiency. A molecular study based on a next-generation PCR sequencing assay reported that mutated PTEN was correlated more frequently with MMR than with proficient MMR [17]. Another critical genetic interaction in ECs and also pre-malignant endometrial hyperplasias seems to be the PTEN/Cyclin D1 deregulation. A study based on their protein expression analysis showed that cyclin D1 overexpression combined with PTEN loss of expression due to mutations characterizes the molecular profile not only of many well differentiated ECs but also of complex hyperplasias with atypia [18]. This should be an evidence of an early event in endometrial carcinogenetic process. PTEN frameshift, nonsense, missense, or silent mutations were detected in both of the previous referred endometrial pathological entities. A molecular study in Iranian females suffering of EC concluded that exon 7 does not play any significant role in the development of the malignancy [19]. Similarly, identification of different PTEN mutations in Taiwanese female population by applying whole-exome sequencing assays enhanced the hypothesis of modified PTEN mutational landscape in ECs, depended on specific target - exons among ethnicities [20].

In conclusion, mutated PTEN suppressor gene is frequently observed in sub-sets of ECs with specific histo-molecular characteristics, especially in Type I cases with MMR deficiency. Additionally, differences in whole genome signatures including oncogenes overactivation in the corresponding female patients affect the aggressiveness of the malignancy and the response rates to novel targeted chemotherapeutic strategies.

Conflict of interests

The authors declare no conflict of interests.

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