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REVIEW PAPER

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Paired box 8 in organogenesis and oncogenesis – a review

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ABSTRACT

Introduction and aim. Paired box 8 (PAX-8) is a specific transcription factor known as a protein product gene that plays an essential role in organogenesis and oncogenesis. The aim of this paper was to discuss structure and function of PAX-8. The aim of this study is to determine the utility of PAX-8 in cytology effusions with metastatic tumor.

Material and methods. This article is a review done in regards to discuss the role knowledge on PAX-8 especially in oncogenesis and organogenesis.

Analysis of the literature. Current information about PAX-8 is presented.

Conclusion. The PAX family of genes plays an important role in the formation of tissues and organs during embryonic development and in maintaining the proper functioning of certain cells after birth

Keywords. oncogenesis, organogenesis, paired box 8, PAX-8, transcription factor

Introduction

Paired box 8 (PAX-8) is a specific transcription factor known as a protein product gene that plays an essential role in organogenesis and oncogenesis. Location of PAX-8 in chromosome 2 is presented in Fig. 1. This gene belongs to the family of paired box transcription factors (PAX). The PAX genes provide instructions for making proteins that attach to specific regions of DNA, and these proteins help to control the activity of particular genes – their expression. Based on this action, PAX proteins are called transcription factors. The PAX family of genes plays an important role in the formation of tissues and organs during embryonic development and in maintaining the normal function of some cells after birth.[1-3] PAX-8 is a transcription factor involved in the regulation of organogenesis of the thyroid, kidneys and paramesonephric ducts (Müllerian ducts).[4-6] PAX-8 releases hormones important for regulating growth, brain development and metabolism. After birth, the PAX-8 protein regulates several genes that are responsible for the production of thyroid hormones.[7-9]

Aim

The aim of this study is to determine the utility of PAX-8 in cytology effusions with metastatic tumor.

Material and methods

This article is a review done in regards to discuss the role knowledge on PAX-8 especially in oncogenesis and organogenesis.

Analysis of the literature

The roles of PAX-8 in oncogenesis are diverse and include epigenetic remodeling, stimulation of proliferation, inhibition of apoptosis, and regulation of angiogenesis. PAX-8 may interact with various protein partners during tumor progression and may exhibit significant function-altering alternative splicing.[10-15] Al-

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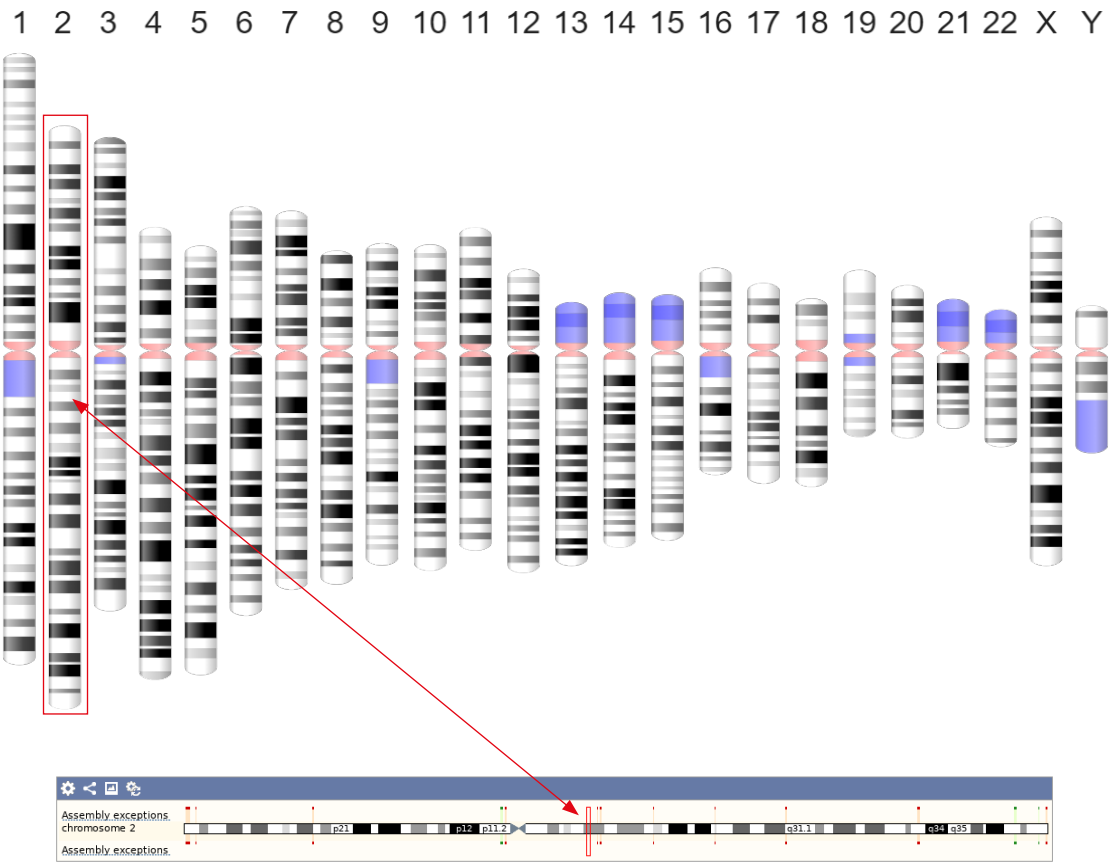

Fig. 1. PAX-8 location

ternative splicing is a fundamental regulatory process of gene expression. Defects in alternative splicing can lead to a variety of diseases, and modification of disease-causing splicing events holds great therapeutic promise.[16-19] Outcome of splicing is often influenced by extracellular stimuli and signaling cascades that converge in RNA-binding splicing regulators. in epithelial tumors of the thyroid and parathyroid glands, kidneys, thymus and female genitals. PAX-8 expression has also been reported in some neuroendocrine neoplasms, including well-differentiated pancreatic neuroendocrine tumors, duodenal and rectal carcinoids, and also in B-cell lymphomas. It has been shown that PAX-8 positivity in these tumors was due to a cross-reactivity of the antibody with the N-terminus region of PAX-6 and PAX-5 respectively. The PAX-8 gene often influences the formation of thyroid tumors (cancers). The abnormal growth then affects individual cells called follicular thyroid cells. Some of these growths, called follicular adenomas, are non-cancerous (benign). Other cancers known as follicular carcinomas are malignant.[21-26]

The combined PAX-8/PPARG gene occurs when the PAX-8 gene on chromosome 2 is linked to the PPARG gene on chromosome 3. The way PAX-8/PPARG influences thyroid follicular cell growth or why some lesions become cancerous while others are benign has not been fully elucidated. On the other hand, it is likely that the joined gene interferes with the normal control of cell division or triggers new cell actions that promote tumor formation. Rearrangements occurring within the PAX-8/PPARG genes most often concern follicular thyroid carcinomas. The PPARG gene encodes a nuclear receptor protein that regulates the expression of genes responsible for glucose and fatty acid metabolism.[26-28] The PAX-8 protein is one of the transcription factors regulating the synthesis of thyroid hormones (functional differentiation markers e.g. Tg, TPO, Slc5a5 and Tshr). As a result of the fusion involving the majority of the coding sequences of both genes, they result in the constant expression of the fusion protein, while maintaining the function of both proteins, which leads to deregulation of the metabolic processes of the cell. PAX-8/PPARG rearrangements are also correlated with lower age of onset and exposure to ionizing radiation.[27] Thyroid dysgenesis is the leading cause of congenital hypothyroidism, a condition characterized by abnormally low levels of thyroid hormones from birth, affecting nearly 1 in 2,000-3,000 newborns worldwide, as the most common endocrine disorder in newborns. PAX-8, expressed at all stages of thyroid follicular cell development, plays a

key role in thyroid morphogenesis through a complex regulatory network.[8]

At least 15 PAX-8 mutations contribute to congenital hypothyroidism, others may only slightly decrease thyroid hormone levels or have no detectable effect. Most mutations change one of the amino acids used to make the PAX-8 protein. Other mutations disrupt protein production, causing an abnormally small version of the PAX-8 protein. Almost all mutations in the PAX-8 gene prevent the PAX-8 protein from binding effectively to DNA. One mutation alters the interactions between the PAX-8 protein and other transcription factors. As a result, the PAX-8 protein cannot fulfill its role in regulating the activity of some genes.[11]

The thyroid gland is extremely small in people with the PAX-8 gene mutation. This finding suggests that mutations in the PAX-8 gene interfere with the normal growth or survival of thyroid cells during embryonic development. As a result, the thyroid gland is reduced in size and may not be able to produce the normal amount of thyroid hormones. Since cases caused by mutations in the PAX-8 gene are caused by a problem with thyroid development, they are classified as thyroid dysgenesis.[17] PAX-8 expression is increased in neoplastic renal tissues, Wilms tumors, ovarian cancer, and Müllerian carcinomas. For this reason, PAX-8 immunodetection is widely used in the diagnosis of primary and metastatic kidney tumors. Reactivation of PAX-8 (or PAX-2) expression has been reported in pediatric Wilms' tumors, nearly all subtypes of renal cell carcinoma, renal adenomas, ovarian, bladder, prostate and endometrial cancer cells. PAX-8 expression is also induced during the development of cervical cancer.[9] Ovarian cancer is one of the most dangerous and widespread gynecological cancers. It is the seventh leading cause of all cancer deaths in the world. High-grade serous cancer (HGSC) accounts for 70% of all ovarian cancer deaths. PAX-8 becomes an important histological marker in most epithelial ovarian cancers as it is present in approximately 90% of cases, especially in HGSC. PAX-8 is necessary for the proper development of the Müller's duct, which includes the fallopian tube, uterus, cervix, and the top of the vagina. In adults, it is expressed in the fallopian tube and uterine epithelium. Considering recent studies that look at events preceding HGSC tumor formation from the fallopian tube, PAX-8 appears to play an important role in the development of ovarian cancer.[10]

PAX genes code for growth regulators that are expressed in a variety of tissues and control critical events in morphogenesis. In kidneys, PAX-8 and PAX-2 are expressed in embryonic development and in certain kidney diseases related to abnormal proliferation (multiplication) of epithelial cells.[11] Genetic and cell biological studies suggest that reducing PAX protein activity in kidney cancer or polycystic kidney disease may slow the progression of these conditions. PAX proteins may be critical for tissue specificity and for epigenetic modifiers that control gene expression and chromatin structure. It may be possible to target PAX proteins to inhibit their function using small molecules. In the absence of effective treatments for kidney cancer and cystic disease, the PAX family of proteins represents new pharmaceutical targets that deserve research and further development.[20-21]

Various previous studies have provided that PAX-8 expression occurs at high levels in specific types of tumor, including thyroid and renal carcinomas and pancreatic neuroendocrine tumors. PAX-8 has been reported to be useful for the detection and differential diagnosis of ovarian carcinoma.[9-10,29]

PAX-8 has been recognized as a potential immunohistochemical marker of pancreatic neuroendocrine tumors. Haynes et al were establishing whether PAX-8 immunohistochemistry can be used as an ancillary marker of pancreatic origin for neuroendocrine tumors. Among welldifferentiated neuroendocrine tumors, only tumors from the pancreas were PAX-8 positive for 56% cases. It can help distinguish pancreatic primary tumors from tumors of other anatomic sites. Among poorly differentiated neuroendocrine carcinomas, PAX-8 expression was identified in all cases of pancreatic and thymic carcinomas.[30]

Metastatic breast carcinoma is known to morphologically mimic primary ovarian carcinoma, resulting in difficulty in distinguishing between these forms of cancer. Study with microarray analysis revealed that PAX-8 and EPAC are expressed at higher levels in ovarian compared with breast cancer.[29,32] Before that WT1 was considered to be a suitable marker to distinguish metastatic breast cancer from ovarian carcinoma. However, WT1 was later observed in focal breast cancer, causing false positive results. By contrast, PAX-8 was stained in none of the breast and almost all ovarian cancer samples, indicating that PAX-8 is a more superior marker for the differential diagnosis of ovarian and breast cancer. [29,31]

Conclusion

Expression of PAX-8 in cancer can serve as a biomarker for diagnostic and prognostic purposes. Due to its limited expression, PAX-8 is a useful immunohistochemical marker with a wide range of diagnostic applications in surgical pathology. Understanding the different mechanisms of action of PAX-8 in development and oncogenesis may identify novel malignancies that currently lack effective therapies.

Declarations

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Author contributions

Conceptualization, M.Sz., DA.; Writing – Original Draft Preparation, M.Sz., DA; Writing – Review & Editing, M.Sz., DA.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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