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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Role of Meteorin-Like Peptide and Asprosin in the Diagnosis of Endometrium Carcinoma

Endometrium Karsinomu Tanısında Meteorin Benzeri Peptit ve Asprosin'in Rolü

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ABSTRACT

Aim: Endometrial Carcinoma (EC) is one of the most common gynecological malignancies in developed countries and the diagnosis is generally suspected according to clinical and radiological findings and confirmed with pathological sampling. Immunohistochemical biomarkers have great importance in the diagnosis. In this study, their roles in the EAC mechanism will be investigated by looking at METRNL and Asprosin levels in Endometrial Adenocarcinoma (EAC).

Material and Method: The patient samples that were obtained from the Pathology Laboratory of Fırat University Faculty of Medicine, Department of Pathology were used in this retrospective study. In this study, 30 patient samples were used. The control group consisted of healthy endometrial tissues of the same patient group. The other group consisted of tissues with Endometrial Adenocarcinoma (EAC) from the same patients. In all groups, the endometrial tissue samples were evaluated immunohistochemically with Meteorin-Like Peptide (METRNL) and Asprosin.

Results: Statistically significant differences were detected between the control and EAC groups in terms of METRNL and Asprosin. METRNL immunoreactivity was found to be higher in EAC tissues than in healthy endometrium tissues ($p<0.001$). Asprosin immunoreactivity was found to be lower in EAC tissues than in healthy endometrium tissues ($p<0.001$).

Conclusion: The results of the present study show that there is a significant relationship between healthy endometrial tissue and EAC in terms of METRNL and Asprosin expression. It is thought that both proteins may be important markers for the diagnosis of EAC.

Keywords: Endometrium, adenocarcinoma, meteorin-like peptide, asprosin

ÖZ

Amaç: Endometriyal Karsinom (EC), gelişmiş ülkelerde en sık görülen jinekolojik malignitelerden biri olup, genellikle klinik ve radyolojik bulgulara göre tanıdan şüphelenilir ve patolojik örnekleme ile doğrulanır. Tanıda immünohistokimyasal biyobelirteçlerin önemi büyüktür. Bu çalışmada ise, Endometrial Adenokarsinomunda (EAC) METRNL ve Asprosin düzeylerine bakılarak, EAC mekanizmasındaki rolleri araştırılacaktır.

Gereç ve Yöntem: Bu retrospektif çalışmada Fırat Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı Patoloji Laboratuvarı'ndan alınan hasta örnekleri kullanıldı. Bu çalışmada 30 hasta örneği kullanıldı. Kontrol grubu aynı hasta grubuna ait sağlıklı endometrial dokulardan oluşturuldu. Diğer grubu ise aynı hastaların EAC olan dokuları oluşturdu. Tüm gruplarda endometrial doku örnekleri Meteorin Benzeri Peptid (METRNL) ve Asprosin ile immünohistokimyasal olarak değerlendirildi.

Bulgular: Kontrol ve EAC grupları arasında METRNL ve Asprosin açısından istatistiksel olarak anlamlı farklılıklar tespit edildi. METRNL immünoreaktivitesi EAC dokularında sağlıklı endometrium dokularına göre daha yüksek bulundu ($p<0.001$). Asprosin immünoreaktivitesi ise, EAC dokularında sağlıklı endometrium dokularına göre daha düşük bulundu ($p<0.001$).

Sonuç: Bu çalışmanın sonuçları sağlıklı endometriyal doku ile EAC arasında METRNL ve Asprosin ekspresyonu açısından anlamlı bir ilişki olduğunu göstermektedir. Her iki proteinin de EAC tanısı açısından önemli belirteçler olabilecekleri düşünülmektedir. .

Anahtar Kelimeler: Endometrium, adenokarsinom, meteorin benzeri peptit, asprosin

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INTRODUCTION

Endometrial Cancer (EC) is one of the most common gynecological cancers ranking third among all cancers in female gender (1,2). The incidence of EC, which poses a great threat to public health, has increased recently (3,4). Early and accurate diagnosis of EC is important for the prevention of this common malignancy and for the survival and quality of life of patients. The diagnosis of precancerous lesions, which are considered Endometrioid adenocarcinomas (EAC), remains problematic because of some histopathological findings and differences of perspective among pathologists, which causes the treatment to be insufficient or more than necessary (5-8). For this reason, early diagnosis and treatment of EC is of great importance in terms of morbidity and mortality.

Also known as Meteorin-like, Meteorin-β, Subfatin, and Cometin, METRNL is a novel secretory protein. Unlike the expression of Meteorin in the Central Nervous System, METRNL is plenty in metabolic organs and barrier tissues (9), with secretion and regulation depending on physiological and pathological conditions. It was demonstrated that METRNL, which is defined as an adipokine, has pleiotropic effects such as regulating insulin resistance over glucose homeostasis, browning of fat tissue and increasing energy production (10). Recent studies suggest that METRNL might have protective roles in many cardio-metabolic and inflammatory diseases. The expression of METRNL might change in different physiological conditions, including exercise, temperature changes, bariatric surgery and high-fat diet. Large-scale investigation of METRNL is important for understanding its importance as a therapeutic and biomarker for some diseases (11).

As a glucogenic hormone secreted in mammalian cells, Asprosin is a 30 kDa protein produced in the C-Terminal Cleavage of Profibrillin (12,13). Asprosin is secreted from adipose tissue. During fasting, Asprosin stimulates gluconeogenesis in the liver and maintains glucose homeostasis over the G protein-coupled receptor (13). It was observed that serum Asprosin levels are elevated in Type 2 Diabetes Mellitus patients, patients with Insulin Resistance and women with Polycystic Ovary Syndrome (PCOS) (12). There are also studies that report that Asprosin is associated with malignancies such as Ovarian CA, basal cell carcinoma, pancreatic cancer, and ductal breast carcinoma (12,14,15). For this reason, Asprosin might be a potential therapeutic target and a promising novel candidate for discovery in the microenvironment of malignancies.

In the present study, the researchers aimed to examine the expression of METRNL and Asprosin in the endometrial epithelial components of the neoplastic tissue in EAC and to investigate if these proteins have roles in the diagnosis of EC.

MATERIAL AND METHOD

Research and Publication Ethics

The study was approved by Fırat University, Local Ethics Committee. The study was conducted with 30 cases from the Pathology Laboratory of Fırat University Faculty of Medicine, Department of Pathology. The Control Group consisted of healthy endometrial tissues of the same patients. The other group consisted of EAC tissues of the same patients. The tissue samples of the groups were treated with METRNL and Asprosin, comparisons were made between the groups, and the results were evaluated.

Immunohistochemistry

Immunohistochemical procedures were performed as described earlier by Kocaman and Artas (16). Immunohistochemistry (IHC) was implemented using histological tissue microarray slides that were 3 µm thick. The following antibodies were used: anti-METRNL antibody (MBS7004241; MyBioSource, San Diego, CA) and anti- Asprosin antibody, FNab09797, Fine Test. A histoscore was calculated for the measurement of tissue levels of meteorin as using indirect immunohistochemical staining.

Microscopic Evaluation of Staining Intensity

The data were utilized and compared separately by 1 blinded independent pathologist and 1 blinded independent histologist based on the extent and intensity of the staining, and a histoscore was determined.

The researchers scored the distribution of staining as 0.1, <25%; 0.4, 26-50 %; 0.6, 51-75%; 0.9, 76-100%, and the intensity of staining as 0, no staining;0.5, very little staining; 1, little staining;2, moderate staining;3, very strong staining. A histoscore was calculated as Histoscore = Distribution × Intensity (16).

Statistical Analysis

The SPSS 22 (IBM Corporation, USA) was employed in the analyses. The One-Way ANOVA Test was used and post-hoc multiple comparisons were made by using the Tukey HSD test. Kolmogorov Smirnov test was used for the normal distribution test. Data are given as mean ± SD and $p<0.05$ was considered statistically significant.

RESULTS

Immunohistochemical Findings

As a result of observing immunohistochemical staining for METRNL and Asprosin immunoreactivity under the light microscope, the following conclusions were reached.

METRNL immunoreactivity was found to be significantly higher in EAC tissues than in healthy endometrium tissues ($p<0.001$) (**Table 1**). METRNL immunoreactivity histoscores of the groups are given in **Figure 1**.

Table 1.METRNL and asprosin immunreactivity histoscore		
Groups	**Control**	**EAC**
METRNL	0,03± 0,02	0,27± 0,05 a
Asprosin	2,55± 0,34	1,03± 0,15 a

Values are given as mean±standard deviation. a. Compared with control (p<0.001).

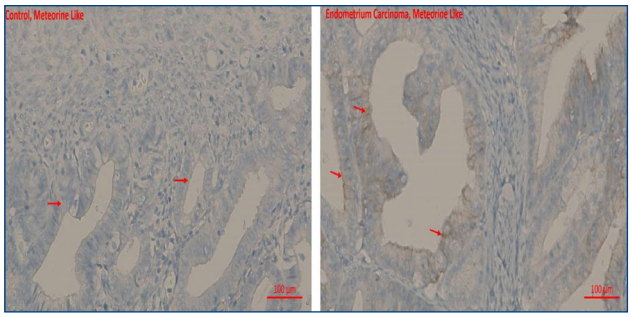

Figure 1. Immunohistochemical analysis of METRNL protein in endometrium, control METRNL immunoreactivity, EAC METRNL immunoreactivity.

Asprosin immunoreactivity was found to be significantly lower in tissues with EAC when compared to healthy endometrial tissues (p<0.001) (**Table 1**). Asprosin immunoreactivity histoscores of the groups are given in **Figure 2**.

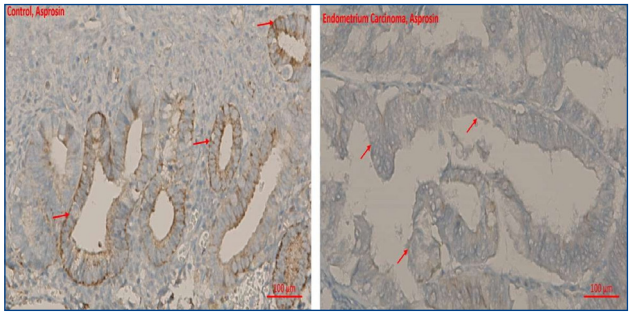

Figure 2. Immunohistochemical analysis of asprosin protein in endometrium, control asprosin immunoreactivity, EAC asprosin immunoreactivity.

DISCUSSION

Early detection of EC is still a critical issue in patient management and in the journey to decrease endometrial cancer-related mortality (17). In the present study that focused on this problem, the researchers examined the expression of METRNL and Asprosin in the endometrial epithelial components of neoplastic tissue in EAC and investigated the roles of these proteins in the diagnosis of EC. As a result of the study, the researchers discovered a significant relationship between healthy endometrium tissue and EAC in terms of METRNL and Asprosin expression and concluded that these proteins might have a diagnostic value regarding EAC.

Although it is necessary to further understand the possible mechanisms by which being overweight might facilitate the development of pathologies such as endometrial and colorectal cancer, the scientific community reported that the main reason might be attributed to pro-inflammatory adipokines that are produced in visceral fat and their relationship with chronic inflammation processes (18). Obesity might also cause phenotypic changes by increasing adipose tissue macrophage production of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin one beta, and monocyte chemoattractant protein) and decreasing the activity of anti-inflammatory cytokines. Hypertrophy of adipose tissue elevates local hypoxia, causes the regulation of different inflammation markers over the action of adipokines, which may increase carcinogenesis by altering cell differentiation and apoptosis (19). About cancer, adipokines might regulate tumor growth, angiogenesis, metastasis, apoptosis, and drug resistance after interacting with various signaling pathways (e.g., NF-κB, JAK/STAT, MAPK, PI3K/Akt, and Wnt/β-Catenin) (20).

In the present study that was conducted on METRNL, which is considered to be an adipokine, the increased expression of METRNL in tissue with EAC when compared to healthy endometrial tissue implies that it might be associated with this tumor. It is also seen in studies conducted on this subject. For example, it was found that as atypia increases in endometrial hyperplasia, the expression of METRNL increases, the highest level being in EAC (21). Studies that investigate the relationship between METRNL and cancer show that it has a protumor effect in pancreatic cancer, and it is emphasized that it might be a prognostic marker for bladder cancer, basal cell Ca, and malignant mesothelioma (14,16,22-24). Although studies are reporting that METRNL is increased in some cancers, more studies are needed to elucidate its mechanism of action because it is a novel molecule. However, what the researchers learned from studies available in the literature is that METRNL can be an important marker in the diagnosis of cancer and a therapeutic target for its treatment.

Some previous studies reported that Asprosin is released in various human cancer types. Asprosin is considered to be an important and promising marker for the early diagnosis of pancreatic cancer (25). A previous study conducted by using immunohistochemical analysis reported that patients who had malignant mesothelioma also had elevated Asprosin immunoreactivity compared to those with reactive mesothelial hyperplasia. It was also reported that fasting plasma Asprosin levels of cancer patients with anorexia were lower at significant levels. However, no significant differences were detected between cancer patients and non-cancer patients (26). It was found that Asprosin is expressed differently in different histological subtypes in ovarian cancer (12). Increasing

evidence show that Asprosin plays roles in regulating the apoptotic mechanism of the cell. It was shown that Asprosin is associated with apoptosis of mesenchymal stromal cells by regulating the ERK1/2-SOD2 pathway (28). Consistent with these results, increased Asprosin levels prevented apoptotic death of cardiac microvascular endothelial cells (29). Asprosin was reported to be differentially expressed in all different histological subtypes of ovarian cancer (12). Apoptosis is a natural defense system against neoplastic growth (27). Previous evidence suggests that Asprosin is involved in the modulation of the cellular apoptotic mechanism. It was shown that Asprosin interferes with the apoptosis of mesenchymal stromal cells by modulating the ERK1/2-SOD2 Pathway (28). Consistent with these reports, increased Asprosin levels reduced apoptotic death of cardiac microvascular endothelial cells (29). In the present study, the decreased expression of Asprosin in tissue with EAC compared to healthy endometrial tissue suggests that it might also be associated with EC. Based on literature data and our study results, we may think that Asprosin has great effects on carcinogenesis, but the limited literature on Asprosin in cancer and apoptosis makes it difficult for us to comment on this issue. However, Asprosin might hold promise for cancer diagnosis and treatment.

The most important limitation of the present study was that it had a retrospective design. Prospective studies with a larger number of patients will be more instructive about the effects of METRNL and asprosin by including the demographic characteristics of the patients. Also, future studies at the molecular level would be better to understand the mechanism of action of these adipokines.

CONCLUSION

In conclusion, the significant change in the expression of METRNL and Asprosin in EAC compared to healthy endometrial tissues indicates that these proteins may be involved in the pathophysiology of EAC. With a clearer understanding of the molecular mechanisms of METRNL and asprosin, they may hold promise in the diagnosis and treatment of EAC in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Fırat University, Local Ethics Committee

Informed Consent: An informed consent form was obtained from the participants before participating in the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics,2021.CA Cancer J Clin 2021;71:7–33.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
3. Constantine GD, Kessler G, Graham S, Goldstein SR. Increased Incidence of Endometrial Cancer Following the Women's Health Initiative: An Assessment of Risk Factors. J Womens Health (Larchmt) 2019;28:237–43.
4. Zhang S, Gong TT, Liu FH, et al. Global, Regional, and National Burden of Endometrial Cancer, 1990–2017: Results From the Global Burden of Disease Study, 2017. Front Oncol 2019;9:1440.
5. Allison KH, Reed SD, Voigt LF, Jordan CD, Newton KM, Garcia RL. Diagnosing endometrial hyperplasia: why is it so difficult to agree? Am J Surg Pathol 2008;32:691–98.
6. Sanderson PA, Critchley HO, Williams AR, Arends MJ, Saunders PT. New concepts for an old problem: the diagnosis of endometrial hyperplasia. Hum Reprod Update 2017;23:232–54.
7. Huang EC, Mutter GL, Crum CP, Nucci MR. Clinical outcome in diagnostically ambiguous foci of 'gland crowding' in the endometrium. Mod Pathol 2010;23:1486–91.
8. Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Value Health 2007;10:183–94.
9. Li ZY, Zheng SL, Wang P et al. Subfatin is a novel adipokine and unlike meteorin in adipose and brain expression. CNS Neurosci Ther 2014;20(4):344–54.
10. Zheng SL, Li ZY, Song J, Liu JM, Miao CY. Metrnl: A secreted protein with new emerging functions. Acta Pharmacol Sin 2016;37(5):571–9.
11. Li Z, Gao Z, Sun T et al. Meteorin-like/ Metrnl, a novel secreted protein implicated in inflammation, immunology, and metabolism: A comprehensive review of preclinical and clinical studies. Front. Immunol 2023;14:1098570.
12. Kerslake R, Hall M, Vagnarelli P, et al. A pancancer overview of FBN1, asprosin and its cognate receptor OR4M1 with detailed expression profiling in ovarian cancer. Oncol Lett 2021;22(3):650.
13. Ovali MA, Bozgeyik I. Asprosin, a C-terminal cleavage product of fibrillin 1 encoded by the FBN1 gene, in health and disease. Mol Syndromol 2022;13(3):175-83.
14. Kocaman N, Yüksel EI, Demir B, Çalık İ, Çiçek D. Two Novel Biomarker Candidates for Differentiating Basal Cell Carcinoma from Trichoblastoma; Asprosin and Meteorine Like Peptide. Tissue Cell 2022;76:101752.
15. Akkuş G, Koyutürk LC, Yılmaz M, Hancer S, Özercan IH, Kuloğlu T. Asprosin and meteorin-like protein immunoreactivity in invasive ductal breast carcinoma stages. Tissue Cell 2022;77:101855.
16. Kocaman N, Artas G. Can novel adipokines, asprosin and meteorin-like, be biomarkers for malignant mesothelioma? Biotechnic & Histochemistry 2020;95:171-75.
17. Chen H, Strickland AL, Castrillon DH. Histopathologic diagnosis of endometrial precancers: updates and future directions. Semin Diagn Pathol 2022;39(3):137–47.
18. Yoon YS, Kwon AR, Lee YK, Oh SW. Circulating Adipokines and Risk of Obesity Related Cancers: A Systematic Review and Meta-Analysis. Obes Res Clin Pract 2019;13:329–39.
19. Doerstling SS, O'Flanagan CH, Hursting SD. Obesity and Cancer Metabolism: A Perspective on Interacting Tumor-Intrinsic and Extrinsic Factors. Front Oncol 2017;7:216.
20. Booth A, Magnuson A, Fouts J, Foster M. Adipose Tissue, Obesity and Adipokines: Role in Cancer Promotion. Horm Mol Biol Clin Investig 2015;21:57–74.

21. Balta H, Kocaman N. The Role of Meteorin-Like Peptide and TRPM2 in Differential Diagnosis in Benign, Premalignant and Malignant Lesions of the Endometrium. FU.Med J Health Sci 2023;3(1):50–55.
22. Manning AA, Zhao L, Zhu Z, et al. IL-39 acts as a friend to pancreatic cancer. Med Oncol 2018;36(1):12.
23. Jung T, Pyun DH, Kim TJ, et al. Meteorin-like protein [METRNL]/IL-41 improves LPS-induced inflammatory responses via AMPK or PPARδ–mediated signaling pathways. Adv Med Sci 2021;66:155-61.
24. Shivakumar M, Lee Y, Bang L, Garg T, Sohn KA, Kim D. Identification of epigenetic interactions between miRNA and DNA methylation associated with gene expression as potential prognostic markers in bladder cancer. BMC Medical Genomics 2017;10(Suppl 1):30.
25. Nam H, Kang S, Park MS, et al. A Serum Marker for Early Pancreatic Cancer with a Possible Link to Diabetes. J Natl Cancer Inst 2022;114(2):228-34.
26. Du C, Wang C, Guan X, et al. Asprosin is associated with anorexia and body fat mass in cancer patients. Support Care Cancer 2021;29(3):1369–75.
27. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144(5):646–74.
28. Zhang Z, Tan Y, Zhu L, et al. Asprosin improves the survival of mesenchymal stromal cells in myocardial infarction by inhibiting apoptosis via the activated ERK1/2-SOD2 pathway. Life Sci 2019;231:116554.
29. Chen S, Wang X, Qiu CM, et al. Study of the Role and Mechanism of Asprosin/Spartin Pathway in Cardiac Microvascular Endothelial Injury Induced by Diabete Mellitus. Sichuan Da Xue Xue Bao Yi Xue Ban 2019;50(6):827–34.