Farabi Tıp Dergisi 2(1): 26-30, 2023
Farabi Medical Journal 2(1): 26-30, 2023

FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

Derleme
Review

https://dergipark.org.tr/tr/pub/farabimedj

SCUBE1 and Irisin Relation in Bladder Cancer

Mesane Kanserinde SCUBE1 ve İrisin İlişkisi

Diler Us-Altay[1*]

[*1]*Ordu University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Ordu, Turkey.*

**Corresponding author e-mail: dilerusaltay@odu.edu.tr*

[1]*https://orcid.org/0000-0002-0465-8403*

ABSTRACT

Bladder Cancer (BC) is a urogenital system disease with a frequency of approximately 11.000 new cases. The major risk factors of BC are smoking and exposure to industrial carcinogens. The diagnosis and monitoring of BC largely consist of invasive tests involving periodic cystoscopy. This method is known as the gold standard although this is a trustworthy method the procedure is highly disturbing for the cancer patient and causes comorbidity. That's why; non-invasive diagnostic methods continue to be researched. Signal Peptide CUB Epidermal Growth Factor 1 Containing Protein (SCUBE1) is a member of the SCUBE family. SCUBE1 is often closely associated with pathological conditions such as thrombus, atherosclerotic plaque, inflammation, and hypoxia-related disorders. Many recent studies have focused on the expression and function of the SCUBE family in cancer. Studies of the SCUBE family have demonstrated the potential to develop as a diagnostic or prognostic biomarker in cancer. Irisin is an adipocytokine produced by proteolytic cleavage of the fibronectin type III domain-containing protein 5 (FNDC5). There are many studies examining the relationship between irisin and cancer. Although SCUBE1 and irisin have been evaluated as early diagnosis biomarkers of bladder cancer in many studies, no study evaluating the parameters together has been found. In the future, multicenter studies evaluating SCUBE1 and irisin parameters together are needed for the early diagnosis of bladder cancer in people who smoke and are exposed to various chemicals.

Keywords: Bladder cancer, Irisin, SCUBE1

ÖZET

Mesane Kanseri (MK) yaklaşık 11,000 yeni vaka sıklığına sahip ürogenital sistem hastalığıdır. Mesane kanserinin başlıca risk faktörleri sigara içmek ve endüstriyel kanserojenlere maruz kalmaktır. MK'nın teşhisi ve izlenmesi büyük ölçüde periyodik sistoskopiyi içeren invaziv testlerden oluşur. Bu yöntem altın standart olarak bilinir, güvenilir bir yöntem olmasına rağmen işlem hasta için oldukça rahatsız edicidir ve komorbiditeye neden olur. Bu nedenle non-invaziv tanı yöntemleri araştırılmaya devam etmektedir. Sinyal Peptit CUB Epidermal Büyüme Faktörü 1 İçeren Protein (SCUBE1), SCUBE ailesinin bir üyesidir. SCUBE1 genellikle trombüs, aterosklerotik plak, inflamasyon ve hipoksi ile ilişkili bozukluklar gibi patolojik durumlarla yakından ilişkilidir. Son zamanlarda yapılan birçok çalışma da SCUBE ailesinin kanserdeki ekspresyonu ve işlevine odaklanılmaktadır. SCUBE ailesi ile ilgili yapılan çalışmalar, kanserde teşhis veya prognostik bir biyobelirteç olarak gelişme potansiyeli olduğunu göstermiştir. İrisin, Fibronektin Tip III Domainini İçeren 5. proteinin (FNDC5) proteolitik bölünmesiyle üretilen bir adipomiyokindir. İrisin ve kanser arasındaki ilişkiyi inceleyen birçok araştırma vardır. SCUBE1 ve irisin, birçok çalışmada mesane kanseri için erken tanı biyobelirteci olarak değerlendirilmesine rağmen parametreleri birlikte değerlendiren bir çalışmaya rastlanılmamıştır. Gelecekte, sigara içen ve çeşitli kimyasalara maruz kalan kişilerde erken mesane kanseri tanısı için SCUBE1 ve irisin parametrelerini birlikte değerlendiren çok merkezli çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Mesane kanseri, İrisin, SCUBE1

Geliş Tarihi/Received Date: 14.11.22 | *Kabul Tarihi/Accepted Date: 05.12.22*

INTRODUCTION

Bladder cancer (BC, BCa) is the second most frequently seen urogenital cancer, involving approximately 350,000 new cases and 150,000 deaths worldwide each year. It is also a major cause of morbidity and mortality. The tumor may sometimes not directly infiltrate the bladder muscle, but due to its high histological grade, this may herald a transition to infiltration of that muscle.[1] First evaluated in the 1950s, tobacco smoking is the most important risk factor for BC development in both men and women and, because of its high prevalence, is responsible for the majority of BC cases.[2] It contains several compounds such as aromatic amines, polycyclic aromatic hydrocarbons, heterocyclic amines, and N-nitroso compounds leading to a DNA damage via single-strand and double-strand DNA breaks, and base modifications. Moreover, the reactive oxygen species present in high concentrations in tobacco smoke, directly induce DNA damage and accumulate in bladder epithelium as result of the metabolism of chemical carcinogens.[3] Bladder cancer is nearly three times more common in smokers than nonsmokers.[4] In addition to bladder cancer, tobacco smoking is strongly associated with increased risk of lung cancer.[5] Chemicals in tobacco increase the expression of proteins involved in inflammation, and activate genetic and epigenetic pathways, thereby adversely affecting the cell cycle through the induction of uncontrolled cell proliferation.[6] BC is a highly complex entity involving various molecular and pathological pathways. Its behavior therefore varies in line with the clinical stage of the tumor and its molecular type. The diagnosis and follow-up of BC largely involve invasive tests involving periodic cystoscopy, a method regarded as the gold standard.[7] Despite being trustworthy, this procedure is distinctly unpleasant for the patient and causes comorbidity. Research into non-invasive diagnostic methods is continuing. In a previous study estimating potential biomarkers in bladder cancer, Sakinewicz et al. reported that podoplanin exhibited 72% sensitivity and 69% selectivity.[8] Tokarzewicz et al. demonstrated that cystatin C exhibited 87% sensitivity and 92% specificity in patients with BC.[9] Wang et al. also reported that bladder cancer-specific antigen-1 exhibits 74% sensitivity and 69% specificity.[10] Interestingly, Guszcz et al. showed that the plasma aromatase biomarker exhibited 100% sensitivity and 100% specificity in their recent study of 78 patients with BC and 18 healthy controls.[11]

Signal Peptide-Cub-Epidermal Growth Factor Domain-Containing Protein 1 (SCUBE1)

SCUBE1 is one of the members of the SCUBE family and a branch of the epidermal growth factor (EGF) superfamily. This has been shown to occur in various domain structures, such as cysteine-rich and EGF-like repeats, and the CUB domain. The SCUBE family consists of three distinct members: SCUBE1, SCUBE2, and SCUBE3.[12] SCUBE1 is a cell surface glycoprotein expressed and released during early embryogenesis and present in both platelet and endothelial cells. SCUBE1 is stored inside alpha granules in inactive platelets. Following activation by thrombin, it shifts to the platelet surface and enters the thrombus through secretion in small-sized soluble particles. Platelets are known to play a significant role between inflammation and thrombosis, and vascular and tissue repair mechanisms. The association between thrombosis and cancer was first set out by Trousseau. Trousseau's syndrome cancer-associated thrombosis) is the second leading cause of mortality in cancer patients after death resulting from cancer itself.[13] The risk of venous thromboembolism is 4-7 times greater in patients with cancer than cancer free individuals.[14] SCUBE1 may indicate hypercoagulability in patients with breast cancer and thus be useful in terms of identifying individuals with a greater risk of thrombosis and requiring anti-thrombotic therapy. SCUBE1 can also be employed as an adjunct test for identifying individuals with a potential risk of breast cancer.[12] A previous study reported significantly higher SCUBE 1 titers in patients with gastric cancer than those in a control group.[15] Karaguzel et al. concluded that SCUBE1 may constitute a promising biomarker in the diagnosis and follow-up of renal tumors.[16] A very recent study by Mentese et al. demonstrated that the sensitivity and specificity of SCUBE1 appear to be quite similar to those of CAIX , an AUC value of 0.879 for SCUBE1 was associated with 71% sensitivity and 92% specificity, while an AUC value of 0.891 for CAIX was associated with 93% sensitivity and 78% specificity. Those authors suggested that increased SCUBE1 levels may be a useful addition to clinical findings of disease in the diagnosis of BC.[7] For the first time in the literature, serum SCUBE1 values in BC patients were found to be statistically higher than in the healthy control group in Mentese and his friends study. The majority of studies to date have concentrated on the expression of the SCUBE family and

its functions in the context of cancer. However, further research into the family's role in other tumors is still needed. Conditional engineered mouse models may yield useful findings concerning the function of SCUBE and the mechanisms involved in its role in cancer progression. There is a need for systematic approaches to screening SCUBE family protein substrates and interactions with other proteins that may yield information regarding their physiological role and mapping in various forms of cancer. Previous research into the SCUBE family has indicated the potential for use as a diagnostic and/or prognostic biomarker in cancer.[17]

Irisin

Irisin is an adipocytokine produced by the proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5). Various recent studies have investigated the relationship between irisin and cancer.[18] Irisin has been shown to activate the adenosine monophosphate-activated protein kinase (AMPK) pathway and to inhibit the mammalian target of rapamycin (mTOR) signaling. Studies have also reported that irisin inhibits pancreatic cancer cell growth via the activation of AMPK, thus downregulating the has occurred in the rate of BC. Early diagnosis is therefore particularly important. SCUBE1 and irisin have been investigated by various researchers as early diagnostic biomarkers in BC, but our search of the literature revealed no studies evaluating these two parameters together.[3,25,26] The ELISA kits used in these studies were designed for research purposes and their diagnostic effectiveness has not been fully confirmed. The sensitivity and specificity of ELISA kits produced by different manufacturers may vary, and differences in absolute values are possible. Similar problems apply to different biochemical parameters. This can be resolved by the development ELISA kits exhibiting high sensitivity and specificity for serum irisin measurement, or through the discovery of high-sensitivity methods capable of measuring irisin levels by high pressure liquid chromatography (HPLC) or LC-MS/MS (Tandem MS). mTOR pathway and suppressing the epithelial-mesenchymal transition (EMT) of pancreatic cancer cells.[19] Moon et al. reported that physiological (5-10 nmol/L) and physiologically/pharmacologically elevated irisin concentrations (50-100 nmol/L) exhibited no effect on cell proliferation or the malignancy potential of obesity-related cancer cell lines in vitro.[20] Us Altay et al. reported that circulating irisin levels increased with the development of GC.[21] Other research reporting increased irisin immunoreactivity in breast, ovary, and cervix carcinoma tissues, and in endometrial hyperplasia suggested that this peptide may be of critical importance during carcinogenesis.[22] Provatopoulou et al. investigated the relationship between irisin and breast cancer and reported significantly lower serum irisin levels in patients with breast cancer than in healthy controls.[23] Aydın et al. employed irisin antibody immunohistochemistry to examine alterations in irisin expression in gastrointestinal cancers compared to healthy tissues. Histoscores (area intensity values) revealed significant increases in irisin levels in gastrointestinal cancer tissues, although not in hepatic cancers.[24] Gaggini et al. reported increased FNDC5/irisin expression in human hepatocellular carcinoma increased.[25] Shoa et al. demonstrated that irisin inhibits lung cell migration, proliferation, and invasion by suppressing epithelial-to-mesenchymal transition.[26] In vivo studies also indicate that irisin may represent an excellent diagnostic factor for cancer.[27,28] Esawy and Abdel-Samd revealed significantly lower levels of serum irisin in patients with BC and postulated that serum irisin concentrations may represent an excellent diagnostic and prognostic marker for BC.[29] Taken et al. also demonstrated that serum irisin levels are capable of employment in the diagnosis of BC. Irisin concentrations can also be of assistance in differentiating high-grade stage tumors.[30] Despite the apparent similarities between Esawy and Taken's studies, there are also some differences. Other malignancies were excluded in Esawy's study, although obesity and other chronic diseases were included, while Taken's study excluded all these diseases. As described above, one particular difficulty with BC is that it cannot be diagnosed early using non-invasive methods.

CONCLUSION AND RECOMMENDATIONS

Evidence demonstrates that the diagnosis of BC, the ninth most common type of cancer worldwide, occurs at a much older age than any other type of cancer. The number of BC cases may be expected to rise in line with life expectancy. The diagnosis and monitoring of BC largely involve invasive tests involving periodic cystoscopy, regarded as the gold standard. Although this is a reliable method, the procedure is a particular source of discomfort for the patient and causes comorbidity.

Table 1. Sensitivity and Specificity of potential biomarkers of BC.

BC biomarkers	Sensitivity	Specificity
SCUBE1[7]	71%	92%
CAIX[7]	93%	78%
Plasma Aromatase Biomarker[11]	100%	100%
Podoplanin[8]	72%	69%
Cystatin C[9]	87%	92%
Bladder cancer-specific antigen-1[10]	74%	69%

Research into non-invasive diagnostic methods is therefore still taking place.

Highlights for future research:

• Evaluation of SCUBE1 and irisin parameters in combination in smoker and non-smoker bladder cancer patients,

• The use of ELISA kits with higher sensitivity and specificity,

• The principal limitation of previous studies is the low number of cancer patients and control cases, and multicenter studies with larger patient series are now needed.

Authorship contribution statement

(Single author) DUA contributed to the conceptualization, data collection, and writing manuscript.

Declaration of competing interest

The author has no potential conflicts of interest to disclose.

Availability of data and materials

All articles used in the current review are available from the corresponding author on reasonable request.

Funding

No financial support was received for this research.

REFERENCES

1. Berthé H , Cissé D, Diallo M, et al. Bladder Cancer: Epidemiological, Clinical and Histopathological Aspects at the University Hospital Point G, Mali. Open Journal of Urology. 2021; 11: 343-350. DOI: 10.4236/oju.2021.1110033.
2. Cumberbatch MG, Rota M, Catto JWF, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. Eur Urol. 2016; 70: 458-466. DOI: 10.1016/j.eururo.2015.06.042.
3. Stern MC, Lin J, Figueroa JD, et al. Polymorphisms in DNA repair genes, smoking, and bladder cancer risk: findings from the international consortium of bladder cancer. Cancer Res. 2009; 69(17): 6857-6864. DOI:10.1158/0008-5472.CAN-09-1091.
4. Zeegers MP, Goldbohm RA, van den Brandt PA. A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). Cancer Causes Control. 2002; 13(1): 83-90. DOI: 10.1023/a:1013954932343.
5. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011; 306(7): 737-45. DOI: 10.1001/jama.2011.1142.
6. Phé V. Bladder Cancer in Neurogenic Patients. World J Urol. 2022; 40(8): 1895-1896. DOI:10.1007/s00345-022-04089-x.
7. Mentese A, Demir S, Ozer Yaman S, Us Altay D, Fidan E, Karaguzel E. Can serum SCUBE1 levels be useful in the diagnosis of bladder cancer? J Exp Clin Med. 2022; 39(2): 525-529. DOI: 10.52142/omujecm.39.2.43
8. Stankiewicz A, Guszcz T, Mena-Hortelano R, Zukowski K, Gorodkiewicz E. Podoplanin serum and urine concentration in transitional bladder cancer. Cancer Biomark. 2016; 16: 343-50. DOI: 10.3233/CBM-160572.
9. Tokarzewicz A, Guszcz T, Onopiuk A, Kozlowski R, Gorodkiewicz E. Utility of cystatin C as a potential bladder tumor biomarker confirmed by surface plasmon resonance technique. Indian J Med Res. 2018; 147: 46-50. DOI: 10.4103/ijmr.IJMR_124_16.
10. Wang Z, Li H, Chi Q, Qiu Y, Li X, Xin L. Clinical significance of serological and urological levels of bladder cancer-specific antigen-1 (BLCA-1) in bladder cancer. Med Sci Monit. 2018; 24: 3882-3887. DOI: 10.12659/MSM.907075.
11. Guszcz T, Szymańska B, Kozlowski R, Lukaszewski Z, Laskowski P, Gorodkiewicz E. Plasma aromatase as a sensitive and selective potential biomarker of bladder cancer and its role in tumorigenesis. Oncol Lett. 2020; 19(1): 562-8. DOI: 10.3892/ol.2019.11080.
12. Topcu TO, Kavgaci H, Ozdemir F, et al. Elevated Serum Levels of SCUBE1, a Marker for Coagulation, in Patients with Breast Cancer. Tohoku J Exp Med. 2015; 237(2): 127-32. DOI: 10.1620/tjem.237.127
13. Ikushima S, Ono R, Fukuda K, Sakayori M, Awano N, Kondo K. Trousseau's syndrome: cancer-associated thrombosis. Jpn J Clin Oncol. 2016; 46(3): 204-8. DOI: 10.1093/jjco/hyv165.
14. Cekic AB, Gonenc Cekic O, Aygun A, et al. The diagnostic value of ischemia-modified albumin (ima) and Signal Peptide-CUB-EGF domain-containing protein-1 (SCUBE-1) in an experimental model of strangulated mechanical bowel obstruction. J Invest Surg. 2022; 35(2): 450-456. DOI: 10.1080/08941939.2020.1847218.
15. Mentese A, Fidan E, Uzun Sumer A, et al. Is SCUBE1 a new biomarker for gastric cancer?, Cancer Biomarkers. 2012; 11(5): 191-195. DOI: 10.3233/CBM-2012-00285.

16. Karagüzel E, Menteşe A, Kazaz IO, et al. SCUBE1: a promising biomarker in renal cell cancer. Int Braz J Urol. 2017; 43: 638-43. DOI: 10.1590/S1677-5538.IBJU.2016.0316.
17. Kumar S, Prajapati KS, Gupta S. The multifaceted role of Signal Peptide-CUB-EGF domain containing protein (SCUBE) in cancer. Int. J. Mol. Sci. 2022; 23(18): 10577. DOI: 10.3390/ijms231810577.
18. Zhang D, Tan X, Tang N, Huang F, Chen Z, Shi G. Review of research on the role of irisin in tumors. Onco Targets Ther. 2020; 13: 4423–4430. DOI: 10.2147/OTT.S245178.
19. Liu J, Song N, Huang Y, Chen Y. Irisin inhibits pancreatic cancer cell growth via the AMPK-mTOR pathway. Sci Rep. 2018; 8(1): 15247. DOI:10.1038/s41598-018-33229-w.
20. Moon HS, Mantzoros CS. Regulation of cell proliferation and malignant potential by irisin in endometrial, colon, thyroid and esophageal cancer cell lines. Metabolism. 2014; 63: 188-93. DOI: 10.1016/j.metabol.2013.
21. Us Altay D, Keha EE, Ozer Yaman S, et al. Investigation of the expression of Irisin and some cachectic factors in mice with experimentally induced gastric cancer. QJM. 2016; 109: 785-90. DOI: 10.1093/qjmed/hcw074.
22. Kuloglu T, Celik O, Aydin S, et al. Irisin immunostaining characteristics of breast and ovarian cancer cells. Cell Mol Biol (Noisy-le-grand). 2016; 62: 40-44.
23. Provatopoulou X, Georgiou GP, Kalogera E, et al. Serum irisin levels are lower in patients with breast cancer: association with disease diagnosis and tumor characteristics. BMC Cancer. 2015; 15: 898. DOI:10.1186/s12885-015-1898-1.
24. Aydin S, Kuloglu T, Ozercan MR, et al. Irisin immunohistochemistry in gastrointestinal system cancers. Biotech Histochem. 2016; 91: 242-50. DOI: 10.3109/10520295.2015.1136988. E
25. Gaggini M, Cabiati M, Del Turco S, et al. Increased FNDC5/Irisin expression in human hepatocellular carcinoma. Peptides. 2017; 88: 62-66. DOI: 10.1016/j.peptides.2016.12.014.
26. Shao L, Li H, Chen J, et al. Irisin suppresses the migration, proliferation, and invasion of lung cancer cells via inhibition of epithelial-to-mesenchymal transition. Biochem Biophys Res Commun. 2017; 485: 598-605. DOI: 10.1016/j.bbrc.2016.12.084.
27. Vliora M, Nintou E, Karligiotou E, et al. Implication of Irisin in different types of cancer: a systematic review and meta-analysis. Int J Mol Sci. 2022; 1: 23(17):9971. DOI: 10.3390/ijms23179971.
28. Kim JS, Galvão DA, Newton RU, Gray E, Taaffe DR. Exercise-induced myokines and their effect on prostate cancer. Nat Rev Urol. 2021; 18(9): 519-542. DOI: 10.1038/s41585-021-00476-y.
29. Esawy MM, Abdel-Samd KM. The diagnostic and prognostic roles of serum Irisin in bladder cancer. Curr Probl Cancer. 2020; 44(4): 100529. DOI: 10.1016/j.currproblcancer.2019.100529.
30. Taken K, Aslan R, Eryilmaz R, Alp HH, Huyut Z, Dönmez Mİ. Serum Irisin is a novel biomarker for bladder cancer detection. Int Urol Nephrol. 2022; 54(1): 55-61. DOI: 10.1007/s11255-021-03074-4.

To Cite: Us-Altay D. SCUBE1 and Irisin Relation in Bladder Cancer. Farabi Med J. 2023; 2(1): 26-30.