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THE ROLE OF SEMAPHORINS IN CANCERS WITH SPECIAL FOCUS ON UROLOGICAL MALIGNANCIES

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Introduction: Semaphorins are multi-function extracellular proteins with signaling properties involved in many processes in the human body. Surprisingly, in carcinogenesis, they may function as promoting or suppressing agents or both at the same time. Semaphorins in the field of urological cancers have been insufficiently studied so far, mainly in prostate cancer. They seem promising markers in urological cancers diagnostics and possibly treatment. This matter is the more worthy of interest since urological cancers are a great medical and economic burden. The review briefly discusses the current state of knowledge about semaphorins in cancers, mainly in urology.

Conclusions: The most investigated cancer was prostate, whereas there is not enough information about semaphorins in bladder cancer and renal cell carcinoma. Apparently, semaphorin 5B exerts a negative influence on renal cell carcinoma, and semaphorins 3A and 4D on bladder cancer. In case of prostate cancer, semaphorins 3B, 3C, 4F are considered to promote neoplasm development. On the other hand, semaphorins 3A and 3E are considered beneficial.

Keywords: semaphorins, cancer, prostate cancer, bladder cancer, renal cell carcinoma, urology

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INTRODUCTION

Malignancies are the primary cause of death of people in developed countries just next to cardiovascular diseases [9]. Considering their great medical, psychological, and economic burden, preventive measures have to be taken. Hence, the search for efficient markers of malignant neoplasms has been conducted ever since to improve early detection of these conditions in order to introduce early treatment and decrease mortality.

The review briefly discusses the current state of knowledge about semaphorins – potential biomarkers – in cancers, mainly in urology.

UROLOGICAL CANCERS

Urological cancers have become an important medical and social problem. The most significant neoplasms in this field of medicine are prostate, bladder and kidney cancers. Among these three, prostate cancer is the most common. Worldwide, its frequency is estimated at about 1,600,000 cases per year and its mortality of 366,000 deaths per year [40]. The main risk factors for this neoplasm are: age (the majority occurs over 65 years old), African-American ethnicity, family history of prostate cancer, fat- and meat-rich diet, supplementation of vitamin D, smoking, obesity, alcohol intake and many others (tab. 1.) [30]. Interestingly, a higher incidence of prostate cancer is observed among fighter pilots. However the exact mechanism is uncertain, it could be explained by the exposure to radiation or harmful chemical substances which can act as carcinogens [5,33,34].

Usually, it presents with no subjective symptoms. Only when it is advanced, it can cause urination disturbances, sexual dysfunction and hematuria [25]. It is diagnosed based on digital rectal examination (DRE), prostate-specific antigen (PSA) blood concentration test, and, in case of abnormalities in these examinations, magnetic resonance imaging (MRI) of the prostate in order to qualify the patient for the prostate biopsy (which remains the gold standard for diagnosis confirmation) in order to perform histopathological examination [10]. The basic treatment is prostatectomy or radiotherapy. In case of advanced disease, local treatment can be combined with the systemic methods (androgen deprivation therapy, chemotherapy, immunotherapy) or systemic therapy can be administered alone. The choice of treatment strategy is based on the presence of metastases. Nowadays there is a new approach proposed, which involves „watchful waiting" strategy and active surveillance first, since this disease is regarded as of indolent course [14].

The second most common urological neoplasm is bladder cancer [27]. There are about 550,000 cases per year worldwide, more frequently in men than women [35,28]. Its main risk factors are exposure to toxic chemical substances and smoking, but also old age, male sex, Caucasian race, excessive body weight, poor diet, and positive family history (tab.1.) [35,37]. Its morbidity is estimated at more than 200,000 deaths annually [35]. The most common symptoms are hematuria, frequent and painful urination [37]. It is diagnosed based on urine cytology and collecting a specimen during cystoscopy for histopathological examination [28]. Therapeutic options depend on the stage of cancer. Primarily, superficial transurethral resection of bladder tumor (TURBT) or, in case of muscle invasive bladder cancer, cystectomy is performed, which is preceded by neoadjuvant chemotherapy. Adjuvant chemotherapy is administered when neoadjuvant chemotherapy was omitted. Radiotherapy is used as a part of tri-modal therapy (along with TURBT and chemotherapy) [37,13].

The third most common urological cancer is renal cell carcinoma (RCC). Its prevalence is estimated to be about 5% of all neoplasms in men and 3% in women globally, therefore it occurs more frequently in men. The main risk factors are age, male sex, obesity, poor diet, and smoking (tab.1.) [6]. Three main symptoms of this cancer, although rarely observed, are hematuria, pain in the lumbar area and palpable tumor. The most frequent

Tab. 1. Risk factors of urological cancers.

Risk factors of urological cancers		
Renal cell carcinoma	**Bladder cancer**	**Prostate cancer**
Age	Smoking	Age
Male sex	Exposure to toxic substances	African-American ethnicity
Obesity	Age	Positive family history
Poor diet	Male sex	Obesity
Smoking	Caucasian race	Fat- and meat-rich diet
	Obesity	Supplementation of vitamin D
	Poor diet	Smoking
	Positive family history	Alcohol

histological type of RCC (about 80%) is clear cell carcinoma [11]. It is diagnosed based on laboratory investigation, CT scan and sometimes tumor biopsy [15].

The above-mentioned malignancies are an essential social issue. Not only are they, taken altogether, very common, especially in the male population (particularly prostate cancer), but also their complications and therapeutic procedures may affect reproductive organs which can result in infertility (e.g. in case of radiotherapy) or impotency in men (in case of prostatectomy). These disturbances are a great psychological burden for patients which undoubtedly worsen their life quality.

SEMAPHORINS

Semaphorins are multi-function extracellular proteins with signaling properties involved in many processes in the human body. Among the wide family of semaphorins, 20 proteins were described and divided into 8 main classes and their distinctive feature is a single cysteine-rich extracellular *sema* domain which determines each protein's properties [1,45]. They are membrane-bound or secreted and can act in the juxtacrine, paracrine or autocrine way [16]. Usually, semaphorins are membrane-anchored or trans-membrane proteins, except for class-3 semaphorins which are secreted proteins [39]. Semaphorins usually bind to two main types of receptors, namely plexins and neuropilins [26]. In the past, semaphorins were regarded as axon guidance molecules. Nowadays it is reported that their functions are much more complex. They are present in most of human body tissues and seem to be engaged in regulating morphology and motility in many different body organs and systems, e.g. nervous, cardiovascular, immune, endocrine, hepatic, renal, reproductive systems, and most importantly, also in cancer cells [1,45].

ROLE OF SEMAPHORINS IN CARCINOGENESIS

Research has shown that many malignant tumors express semaphorins as well as their receptors [16]. The role of semaphorins in cancer development has been already investigated. Their involvement in carcinogenesis was established e.g. in lung cancer, ovarian cancer, endometrial cancer, breast cancer or oral squamous cell carcinoma and melanoma [26]. Interestingly, semaphorins can act in a positive or negative way in the carcinogenesis, depending on their type, and even some of them possess double properties.

Proteins such as semaphorin (sema) 3F and sema3B play a beneficial role in this matter, as they have been proven to have a suppressing influence on tumor growth. They can inhibit cell proliferation, as well as angiogenesis, and therefore stop tumor progression and spread outside the primary site of origin. For instance, their properties have been investigated in esophageal squamous cell carcinoma. One study has shown that sema3F can be a potential prognostic marker since its expression is associated with overall survival and lymphatic metastases [44]. The beneficial role of sema3F has also been established in colorectal cancer because of its ability to inhibit the growth and metastatic potential of this neoplasm [32]. Moreover, in patients with osteosarcoma in whom lower expression of sema3F was found, a worse prognosis was determined [23]. As for sema3B its downregulation has been linked to worse prognosis in hepatocellular carcinoma, therefore the suggestion of its use as a prognostic biomarker [20]. In addition, its positive role in tumor growth suppression has been determined in lung and breast cancer [7].

On the other hand, sema5A, sema7A or sema4D have the exact opposite effect on tumor growth, since they influence the promotion of malignant cell proliferation and angiogenesis. For example, studies have shown that sema5A is associated with the progression of pancreatic, gastric, as well as cervical cancer, in which it has been even suggested as a marker of unfavorable prognosis [43,29]. Sema7A has been associated with the promotion of metastases of melanoma, squamous cell carcinoma and breast cancer. Sema4D has been linked to the progression of various neoplasms, such as head and neck tumors, breast, ovarian cancer and pancreatic cancer or osteosarcoma [26].

Finally, sema3A, *sema3C*, sema3E and sema6A can either inhibit, or promote tumor progression, which could be explained by complex molecular relationships between these proteins and their receptors, as well as their modification [26]. Sema3A, on one hand, is considered to inhibit angiogenesis due to competition with VEGF for receptors in endothelium and suppress the tumor progression. On the other hand, increased levels of this protein have been reported in subjects with pancreatic cancer, glioblastoma multiforme and liver cancer of poor prognosis [42]. Sema3C is mostly perceived as a procancerous semaphorin, because it is able to stimulate cell proliferation,

migration and VEGF secretion in endothelium, as well as inhibit apoptosis [2]. However, there are some reports of its anti-angiogenic potential. Sema3E is an intriguing semaphorin since it binds to the plexin-D1 receptor as a signal-transducing receptor, which can further associate with neuropilins to transduce signals of other class-3 semaphorins leading to altered responses of cells to sema3E [26]. Hence, it may exert various influence. It has been reported to inhibit angiogenesis [36], at the same time as promoting metastases [8]. Sema6A function seems different regarding the particular kind of tumor. It is able to suppress angiogenesis inhibiting the neoplasm growth and there are reports on longer survival of patients with glioblastoma expressing higher sema6A protein levels. On the contrary, attempts to silence its expression result in increased apoptosis and reduced angiogenesis which would indicate its tumor-promoting properties [26].

ROLE OF SEMAPHORINS IN UROLOGICAL CANCERS

Semaphorins in the field of urological cancers have been insufficiently studied so far. Considering the current state of knowledge regarding semaphorins' activity in the three analyzed cancers, namely prostate, bladder and renal cell carcinoma, these proteins have been investigated predominantly in prostate neoplasm, and much less often in the other two (tab. 2.).

Prostate cancer

Malignant transformation of prostate epithelium begins when the paracrine mechanism of andromedins action on epithelial cells switches to an autocrine way resulting in their excessive growth. What is known about the semaphorins' role in prostate cancer is that there is a *sema3C* gene induced by androgens with an androgen receptor-induced enhancer containing an androgen response element in intron 2 of *sema3C*. Sema3C stimulates cancer growth by transactivation of multiple receptor tyrosine kinases (e.g. EGFR, HER2 and MET via Plexin B1). Moreover, *sema3C* appears to be a soluble androgen-induced autocrine growth factor in prostate cancer. Considering its role in this malignancy, *sema3C* has been suggested as a potential future therapeutic target in prostate cancer, especially when cancer becomes resistant to castration [18]. Tam et al. discovered that *sema3C* is able to promote the process called epithelial-to-mesenchymal transition (EMT) in prostate cells, which leads the cells to lose the intracellular attachment, become more loose and cancerous. Tam et al. proved *sema3C* ability to stimulate migration and invasion of cells in vitro, as well as cell dissemination in vivo [38]. It appears that *sema3C* is upregulated in prostate cancer tissue [38, 4] which initiates alterations in cell characteristics [38].

Sema4F has been established as a marker of aggressive prostate cancer. Ding et al. observed that sema4F regulates neuroepithelial interactions which are crucial for cancer growth, cell migration and metastases. Apparently, sema4F is also predictive of tumor progression. Subjects with higher expression of sema4F had an increased risk of biochemical recurrence, moreover this protein was at the same time an independent indicator for recurrence. Besides the predictive value of sema4F, it could also become a therapeutic target [12].

As for sema3A, it seems to have two-faceted nature. On one hand, its decreased levels have been found in prostate cancer and it has been perceived as a potentially suppressive agent [21]. On the other hand, sema3A is able to influence bone metabolism and promote the differentiation of pre-osteoblastic cells. Liu et al. have shown that prostate cancer-induced osteoblastic differentiation is partially mediated by sema3A, which may contribute to the development of a new therapeutic strategy [22].

Sema3E has abnormal, higher expression in the prostate cancer tissue compared to healthy prostate. It is able to regulate the adhesion and motility of cancer cells. Sema3E has been proven to

Tab. 2. The potential (positive or negative) influence of semaphorins investigated so far with regards to specific type of cancer.

Semaphorins investigated so far in urological cancers		
Cancer	**Negative influence**	**Positive influence**
Renal cell carcinoma	Semaphorin 5B	-
Bladder cancer	Semaphorin 3A Semaphorin 4D	-
Prostate cancer	Semaphorin 3B Semaphorin 3C Semaphorin 3F Semaphorin 4F	Semaphorin 3A Semaphorin 3E Semaphorin 3F

decrease the adhesion of several prostate cancer cell lines and increase others. At the same time, it inhibits the migration of the majority of prostate cancer cell lines [4]. Sema3E has been also observed to be downregulated by hypoxia in prostate cancer, similar to sema3A, which suggests they act as anti-angiogenic factors in this type of cancer [12].

Sema3F has been found to be decreased in cancer tissue compared to healthy prostate [41]. Beuten et al. investigated polymorphisms in sema3B and sema3F in prostate cancer in regard to patients' ethnicity. Polymorphisms in sema3B and sema3F are apparently associated with an increased risk of prostate cancer, as well as poor prognosis in Hispanic and non-Hispanic white men [3].

Li et al. analyzed several semaphorins altogether and discovered that sema3A, sema3B, sema3E and *sema3C* staining could become independent predictors of biochemical recurrence after radical prostatectomy in low and intermediate risk cancer [21].

Bladder cancer

Less information can be found regarding bladder cancer and its associations with semaphorins. Higher tissue expression and urine concentrations of sema3A were found among patients with urothelial cancer, interestingly only in men, which points to this protein as a potential cancer biomarker [42].

Sema4D (CD100) is physiologically expressed in the immune system cells [31]. Its role in autoimmune, allergic diseases and cancers has been well-documented. Sema4D has been investigated in bladder cancer in the study conducted by Lu et al. They observed overexpression of this protein in neoplastic bladder tissues compared to healthy ones. Sema4D seems also to have an influence on cell turnover. When sema4D was knock downed, there was an increased apoptosis, as well as a reduced proliferation rate of bladder epithelial cells and their motility. When overexpression of sema4D occurred, the exact opposite happened. Moreover, similar to *sema3C* in case of prostate cancer, sema4D is able to promote EMT in bladder cancer cells. An open question remains whether sema4D stimulates angiogenesis in bladder cancer cells [24].

Renal cell carcinoma

As for the renal cell carcinoma, the data is scarce. To the best of our knowledge, the only investigated semaphoring so far is *sema5B*, and the data are contradictory. Sema5B apparently promotes cell viability of clear cell renal carcinoma [16]. Kundu et al. suggested that PRDM16 (PR [PRD1-BF1-RIZ1 homologous] domain–containing 16), which appears to be silenced in RCC, has its role in the suppression of the HIF-responsive gene of *sema5B*. Hence, they proposed *sema5B* as a tumor-stimulating agent. Besides, they also found a low expression of sema5A in RCC [19]. Kundu's observations are supported by Hirota et al. who proved that the lower *sema5B* expression in RCC cells impairs RCC cell viability [17]. A slightly opposite point of view was presented by Ding et al. In the clear cell carcinoma, admittedly, there was an increased *sema5B* expression that has been linked to immune cell infiltration, whereas increased *sema5B* mRNA expression was significantly correlated with sex, age, tumor stage, pathologic stage, and histologic grade. Considering the above, *sema5B* has been proposed as a new biomarker of RCC, similar to previous studies, however associated with favorable prognosis [11].

CONCLUSIONS

Semaphorins have been insufficiently studied in the field of urology so far, especially in case of bladder and renal cell cancer. At the same time, they seem promising markers in urological cancers diagnostics and possibly treatment. Considering numerous types of semaphorins and their various properties, their use in clinical practice requires more in-depth investigation. Every semaphorin should be studied separately with regards to particular urological cancer in order to establish their specific characteristics and potential use in daily clinical practice.

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REFERENCES

1. Alto LT, Terman JR. Semaphorins and their Signaling Mechanisms. Methods Mol Biol. 2017; 1493:1-25.
2. Banu, N., Teichman, J., Dunlap-Brown, M., Villegas, G. & Tufro, A. Semaphorin 3C regulates endothelial cell function by increasing integrin activity. FASEB J 2006; 20: 2150–2152.
3. Beuten J, Garcia D, Brand TC, et al. Semaphorin 3B and 3F single nucleotide polymorphisms are associated with prostate cancer risk and poor prognosis. J Urol. 2009; 182:1614-20.
4. Blanc V, Nariculam J, Munson P, et al. A role for class 3 semaphorins in prostate cancer. Prostate. 2011; 71:649-58.
5. Buñay J, Kossai M, Damon-Soubeyrant C, et al. Persistent organic pollutants promote aggressiveness in prostate cancer. Oncogene. 2023; 42:2854-2867.
6. Capitanio U, Bensalah K, Bex A, et al. Epidemiology of Renal Cell Carcinoma. Eur Urol. 2019; 75:74-84.
7. Castro-Rivera E, Ran S, Brekken RA, Minna JD. Semaphorin 3B inhibits the phosphatidylinositol 3-kinase/Akt pathway through neuropilin-1 in lung and breast cancer cells. Cancer Res. 2008; 68:8295-303.
8. Christensen CR, Klingelhofer J, Tarabykina S, Hulgaard EF, Kramerov D, Lukanidin E. Transcription of a novel mouse semaphorin gene, M-semaH, correlates with the metastatic ability of mouse tumor cell lines. Cancer Res 1998; 58:1238-44.
9. Death cause statistics available at: https://www.cdc.gov/nchs/fastats/deaths.html, accessed on May 3rd 2023.
10. Descotes JL. Diagnosis of prostate cancer. Asian J Urol. 2019; 6:129-136.
11. Ding J, Zhao S, Chen X, et al. Prognostic and Diagnostic Values of Semaphorin 5B and Its Correlation With Tumor-Infiltrating Immune Cells in Kidney Renal Clear-Cell Carcinoma. Front Genet. 2022; 13:835355.
12. Ding Y, He D, Florentin D, et al. Semaphorin 4F as a critical regulator of neuroepithelial interactions and a biomarker of aggressive prostate cancer. Clin Cancer Res. 2013; 19:6101-11.
13. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer, available at: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. Accessed on 20/01/2024.
14. European Association of Urology Guidelines on Prostate Cancer, available at: https://uroweb.org/guidelines/prostate-cancer. Accessed on 20/01/2024.
15. Gray RE, Harris GT. Renal Cell Carcinoma: Diagnosis and Management. Am Fam Physician. 2019 Feb 1;99(3):179-184. Erratum in: Am Fam Physician. 2019; 99:732.
16. Gurrapu S, Tamagnone L. Transmembrane semaphorins: Multimodal signaling cues in development and cancer. Cell Adh Migr. 2016; 10:675-691.
17. Hirota E, Yan L, Tsunoda T, et al. Genome-wide gene expression profiles of clear cell renal cell carcinoma: identification of molecular targets for treatment of renal cell carcinoma. Int J Oncol. 2006; 29:799-827.
18. Hui DHF, Tam KJ, Jiao IZF, Ong CJ. Semaphorin 3C as a Therapeutic Target in Prostate and Other Cancers. Int J Mol Sci. 2019; 20:774.
19. Kundu A, Nam H, Shelar S, et al. PRDM16 suppresses HIF-targeted gene expression in kidney cancer. J Exp Med. 2020; 217:e20191005.
20. Li GZ, Shen D, Li GH, et al. Decreased expression of serum semaphorin 3B is associated with poor prognosis of patients with hepatocellular carcinoma. Exp Ther Med. 2021; 21:236.
21. Li K, Chen MK, Li LY, et al. The predictive value of semaphorins 3 expression in biopsies for biochemical recurrence of patients with low- and intermediate-risk prostate cancer. Neoplasma. 2013; 60:683-689.
22. Liu F, Shen W, Qiu H, Hu X, Zhang C, Chu T. Prostate cancer cells induce osteoblastic differentiation via semaphorin 3A. Prostate. 2015; 75:370-80.
23. Liu MH, Fu WJ, Cui YH, Guo QN, Zhou Y. Downregulation of Semaphorin-3F is associated with poor prognostic significance in osteosarcoma patients. Am J Cancer Res. 2016; 6:2252-2262.
24. Lu JJ, Su YW, Wang CJ, Li DF, Zhou L. Semaphorin 4D promotes the proliferation and metastasis of bladder cancer by activating the PI3K/AKT pathway. Tumori. 2019; 105:231-242.
25. Merriel SWD, Funston G, Hamilton W. Prostate Cancer in Primary Care. Adv Ther. 2018; 35:1285-1294.
26. Neufeld G, Mumblat Y, Smolkin T, et al. The role of the semaphorins in cancer. Cell Adh Migr. 2016; 10:652-674.
27. Nevedomskaya E, Baumgart SJ, Haendler B. Recent Advances in Prostate Cancer Treatment and Drug Discovery. Int J Mol Sci. 2018; 19:1359.

28. Oeyen E, Hoekx L, De Wachter S, Baldewijns M, Ameye F, Mertens I. Bladder Cancer Diagnosis and Follow-Up: The Current Status and Possible Role of Extracellular Vesicles. Int J Mol Sci. 2019; 20:821.

29. Pan G, Zhu Z, Huang J, et al. Semaphorin 5A promotes gastric cancer invasion/metastasis via urokinase-type plasminogen activator/phosphoinositide 3-kinase/protein kinase B. Dig Dis Sci. 2013; 58:2197-204.

30. Perdana NR, Mochtar CA, Umbas R, Hamid AR. The Risk Factors of Prostate Cancer and Its Prevention: A Literature Review. Acta Med Indones. 2016; 48(3):228-238.

31. Rajabinejad M, Asadi G, Ranjbar S, et al. Semaphorin 4A, 4C, and 4D: Function comparison in the autoimmunity, allergy, and cancer. Gene. 2020; 746:144637.

32. Rao J, Zhou ZH, Yang J, et al.Semaphorin-3F suppresses the stemness of colorectal cancer cells by inactivating Rac1. Cancer Lett. 2015; 358:76-84.

33. Raslau D, Abu Dabrh AM, Summerfield DT, Wang Z, Steinkraus LW, Murad MH. Prostate cancer in pilots. Aerosp Med Hum Perform. 2016; 87:565-570.

34. Rogers D, Boyd DD, Fox EE, et al. Prostate cancer incidence in U.S. Air Force aviators compared with non-aviators. Aviat Space Environ Med. 2011; 82:1067-1070.

35. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. Med Sci (Basel). 2020; 8:15.

36. Sakurai A, Gavard J, Annas-Linhares Y, et al. Semaphorin 3E initiates anti-angiogenic signaling through Plexin-D1 by regulating Arf6 and R-Ras. Mol Cell Biol 2010; 30:3086-98.

37. Smolensky D, Rathore K, Cekanova M. Molecular targets in urothelial cancer: detection, treatment, and animal models of bladder cancer. Drug Des Devel Ther. 2016; 10:3305-3322.

38. Tam KJ, Hui DHF, Lee WW, et al. Semaphorin 3C drives epithelial-to-mesenchymal transition, invasiveness, and stem-like characteristics in prostate cells. Sci Rep. 2017; 7:11501.

39. Toledano S, Nir-Zvi I, Engelman R, Kessler O, Neufeld G. Class-3 Semaphorins and Their Receptors: Potent Multifunctional Modulators of Tumor Progression. Int J Mol Sci. 2019; 20(3):556.

40. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. Genes Dev. 2018; 32(17-18):1105-1140.

41. Wu G. Clinical relevance of semaphorin-3F in patients with prostate cancer. Clin Invest Med. 2019; 42:E64-E69.

42. Vadasz Z, Rubinstein J, Bejar J, Sheffer H, Halachmi S. Overexpression of semaphorin 3A in patients with urothelial cancer. Urol Oncol. 2018; 36:161.e1-161.e6.

43. Xiao JB, Li XL, Liu L, et al. The association of semaphorin 5A with lymph node metastasis and adverse prognosis in cervical cancer. Cancer Cell Int. 2018; 18:87.

44. Xie Z, Li T, Huang B, Liu S, Zhang L, Zhang Q. Semaphorin 3F Serves as a Tumor Suppressor in Esophageal Squamous Cell Carcinoma and is Associated With Lymph Node Metastasis in Disease Progression. Technol Cancer Res Treat. 2020; 19:1533033820928117.

45. Yazdani U, Terman JR. The semaphorins. Genome Biol. 2006; 7:211.

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