RESEARCH AND CLINICAL MEDICINE JOURNAL
The European Journal of Innovative, Integrative and Translational Medicine
Volume IV, Issue 4, 2020

Upper Urinary Tract Urothelial Carcinoma: Molecular Profile and Possible Biomarkers for Targeted Therapy

Ovidiu Cătălin Ferician[1,2], Adela Maria Ferician[1,2], Alin Cumpănaș[1,2]
[1]Victor Babes University of Medicine and Pharmacy, Department of Orthopedics, Traumatology, Urology and Medical Imaging, Timisoara, Romania
[2]Clinic of Urology, Timisoara, Romania

REVIEW

Abstract

Upper urinary tract urothelial tumours represent more than 5 to 10% of all urothelial tumours. Bladder urothelial tumours represent the majority of the cases and this tumour type is well characterized from both the pathologic and molecular point of view. Although there are many similarities between the two tumour types, the development and the prognosis of these diseases are different. Upper urinary tract urothelial tumours tend to be more aggressive and with a poorer prognostic. Today, many treatment regimens for upper urinary tract urothelial tumours derives from bladder tumours knowledge. We need a better understanding of the molecular behaviour, tumour biomarkers and possible targets for the treatment of upper urinary tract urothelial tumours. This review aims to gather current knowledge regarding this aspect.

Keywords: upper urinary tract urothelial tumour, cell cycling, tumour suppressor gene, transcription factor.

I. INTRODUCTION

Upper tract urothelial carcinomas (UTUC) consist of 5-10% of all urothelial cancers (UC) [1]. UTUC develops from the urothelium of the ureter and renal collecting system (pelvis and calix). Today we have a better understanding of the behaviour of bladder urothelial carcinomas (UBUC) but we cannot say the same for UTUC. UTUC seems to be more aggressive than UBUC and with a lower prognostic rate [2].

In the last years, the treatment for UBUC is expanding, but on the other hand we don`t have clear recommendations for pre or post-operatory therapy regimens for UTUC [3]. Moreover, we have some similarities between UBUC and UTUC in terms of morphologic and cytogenetic changes but controversy remains in their biological behaviour [4].

The Cancer Genome Atlas (TCGA), based on molecular studies, classified UBUC into five molecular subtypes: luminal-papillary, luminal-infiltrated, luminal, basal/squamous, and neuronal. As a particular notice, UTUC was not included in this classification [5]. Because of these molecular findings, cisplatin-based therapy seems appropriate for UBUC [6]. Recently immune therapy is considered for muscular invasive urothelial cancers (UBUC) [7]. There is an association between immune checkpoint inhibitors, response and, survival and, this allowed the TCGA classification and also potential biomarkers as targets in the treatment of UC [8].

There are some similarities between UBUC and UTUC but also some notable differences[9] and in order to understand these differences, we need a better molecular approach. These review focuses particularly on molecular components that can make the difference between selected cases, and on the other hand to move the knowledge on urothelial carcinoma beyond the already classical immunohistochemical portrait. The aim of this review is to update our knowledge about the molecular and biological behaviour of UTUC and also about possible targets for therapy.

II. POTENTIAL BIOMARKERS

ALDH2, CCNE1, and SMAD3

ALDH2 (aldehyde dehydrogenase**)** has an important role in multiple metabolic functions, CCNE1(cyclin E1) and SMAD3(mothers against decapentaplegic homolog 3) are involved in the regulation of the cell cycling and growth signal transduction. The deregulation of these three genes is leading to disruption of different cell function as cell cycle, metabolism, and growth. The expression of CCNE1 and

Corresponding author: Ovidiu Ferician
Address: Timișoara Emergency County Hospital, Bd. Liviu Rebreanu, Nr.156, Timișoara, Romania
Phone: +40744933798 Email: ovidiu.ferician@gmail.com

SMAD3 is high in the tumour tissue as compared with the normal. The expression of ALDH2 is high in normal tissue as compared with the tumour. Low ALDH2 expression is correlated with high CCNE1 and SMAD3 expression and with an increase in tumour depth. High expression of CCNE1 and SMAD3 and low expression of ALDH2 are correlated with adverse outcomes. The expression of these factors can identify high-risk patients in the T3, T4 group. It seems that the expression of these proteins can be independent prognostic markers for patients with UTUC [10], but current results need further validation on larger series.

CCAAT/enhancer-binding protein delta (CEBPD)

CEBPD is a transcription factor with a role in cell metabolism, differentiation, growth, and cell death [11]. Initially, this protein was correlated with suppression activity in different types of tumours [12], but recent studies have shown promoting metastasis and chemotherapy resistance in UC [13]. CEBPD is overexpressed and amplified in UTUC and is associated with T stage, high grade, nodal invasion, vascular and perineural invasion, and mitotic activity. Moreover, it is strongly predictive for poor prognosis, multifocality, nodal metastasis, and perineural invasion. CEBPD promotes the migration and invasion of UC cells by binding to the MMP2 (matrix metalloproteinase) leading the transcriptional upregulation. The co-expression of CEBPD-MMP2 correlated with pT status, nodal metastasis, vascular and perineural invasion, and high mitotic activity, thus a more aggressive behaviour. It seems that CEBPD has an oncogenic role in UC by enhancing the invasiveness of UC cells [14], and therefore it should be taken into account as prognostic marker but its involvement in therapy still remains obscure.

Genomic alteration

UBUC and UTUC share similar molecular characteristics but they have also site-specific features. The main molecular alteration in both cases are TP53(tumor protein p53**)**, PIK3CA(phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), and FGFR3(fibroblast growth factor receptor 3) [15]. TP53 mutation was the most frequent compared with FGFR3 mutation. TP53 is correlated with high grade and stage whereas FGFR3 with low grade [16]. Another mutation which will require future investigation is the KDR(kinase insert domain receptor) gene mutation that encodes VEGFR2(vascular endothelial growth factor receptor 2) [17]. RB1(retinoblastoma 1) mutation is correlated significantly with UBUC and to a smaller degree with UTUC (9). Another gene alteration is the amplification of NOTCH1(neurogenic locus notch homolog protein 1) and FGFR3 which can be an important therapeutic target [18]. Besides FGFR3, in UBUC, it is also found the expression of FGFR1, which is implicated in the stimulation of cell proliferation and migration via the activation of the MAPK(mitogen-activated protein kinase) pathway [19].

SLIT3-mIR-34a-5p

SLIT3(slit homolog 3 protein), a member of the SLIT gene family is encoding the secretion of glycoproteins related to kinases and microtubule cytoskeleton [20]. SLIT3 is a tumour suppressor gene and its expression is reduced in many types of cancers. The reduction is due to the hypermethylation of the promoter region and inhibition by intrinsic mIR-218 [21]. SLIT3 expression is reduced in high-grade UBUC and UTUC tumours and this is correlated with poor prognostic.

A miRNA exosome is a tool through which the tumour cells cross-talk with the microenvironment cells to promote invasion [22]. mIR-34a is a tumour suppressor miRNA involved in cell cycle and apoptosis through p53-dependent and independent pathways, which is silenced in many cancer cells including UC cells [23]. High expression of mIR-34a is correlated with reduced recurrence rates in UBUC, with reduced activity of cancer stem cells, and with high sensitivity of these cells to chemotherapy [24, 25]. mIR-34a-5p is strongly expressed in UTUC, and SLIT3-mIR-34a-5p regulation seems to have a regulatory role in UTUC [26]. We must question in the near future that interfering this pathway has some therapeutic benefit in experimental model and potentially, in patients with urothelial carcinoma.

FGFR3-T cell-depleted UTUC

In the majority of the cases, sporadic UTUC is T-cell depleted. FGFR upregulation is also correlated with the depletion of T-cell in pancreatic and breast tumours [27]. High expression of FGFR3 has already been highlighted in UBUC [28]. Inhibition of FGFR3 expression is increasing BST2(bone marrow stromal antigen 2), a viral restriction factor induced by interferon [29]. FGFR3 is involved also in Y701-antibody inhibition, a key factor for STAT1(signal transducer and activator of transcription 1) activation [30]. FGFR3 inhibition is stimulating the upregulation of interferon-induced genes to reduce the T-cell depleted phenotype. Moreover, combination therapy, including FGFR3 inhibitors, and immune checkpoint inhibitors seems to be a feasible therapeutic strategy. Today, we have ongoing clinical trials combining Erdafinib with BGJ398-inhibitor in different cancer types with FGFR high expression, among them also UC, with encouraging results [31,32,33].

DPP4/CD26

Dipeptidyl peptidase (DPP) 4 is a transmembrane glycoprotein from the serin peptidase family and is upregulated in many tumours and also in UTUC [34]. DPP is expressed on the surface of many cell types such as lymphocytes, endothelial and epithelial cells. The role of this protein is ECM(extracellular matrix) and adenosine deaminase (ADA) binding and serin peptidase activity. Consequently, it is involved in the inflammatory and immunological response, signal transduction and apoptosis through chemokine and cytokine degradation. DPP4 can regulate the tumour cells growth through IL-6R(interleukin-6 receptor) [35] and promotes cell adhesion, invasion and cycle arrest [36]. High expression of DPP4 was observed in melanoma,

gynaecological cancers, hematologic cancers and renal cell carcinomas [37]. To increase the metastatic potential, DPP4 stimulates epithelial cell transformation and tumour cell adhesion through MEK/ERK(Ras-Raf-MEK-ERK pathway) and JNK/c-Jun(c-Jun N-terminal kinases**)** signalling pathway and also E2F1(transcription factor E2F1) activity [38]. Another mechanism involved in tumour migration is the degradation of the extracellular matrix, DPP4 seems to be involved in these processes by binding fibronectin and ADA {39, 40].

The activity of DPP4 is different depending on the multiple non-physiological states. The expression is increased in endometrial carcinoma, but with inverse correlation to tumour grade, is increased in pleural mesothelioma but correlated with improved survival, is increased in ovarian carcinoma but involved in the positive response to chemotherapy [36, 40, 41]. For now, these apparently controversial data in different types of malignant tumour limit the application of these marker in the prognosis and therapy. The serum levels of DPP4 is decreased in cancer patients and is correlated with lower survival. This is because the major source of serum DPP4 is the T lymphocytes and their levels are influenced by the T-cell tumour tolerance [42]. Also, the inhibition of DPP4 will increase CD4 and CD8 T lymphocytes and prolongs survival [43]. Based on the current data, the expression of DPP4 in UTUC and UBUC is increased and is correlated with cell proliferation, invasion and migration. In the near future it is likely that DPP4 will be used as in targeted therapy and also as a prognostic marker [44].

MCM10

MCM10 (chromatin-associated protein) is a replication initiation protein that interacts with MCM2-7 complex. Is involved in the DNA replication in human cells by recruitment of protein A and DNA polymerases at the origins [45-48]. The depletion of MCM10 and the interaction between MCM10 and BRCA2 (breast cancer 2 gene) are involved in the tumorigenesis by severe defects in DNA double-strand break repair process [9, 50]. Strong expression of MCM10 is correlated with aggressive UTUC and UBUC, with worse outcome in cancer-specific survival and metastatic risk. MCM10 can be an early sign of poor prognostic in UC, also can be a target for therapy. These anti-MCM10 molecules can inhibit tumour cells by blocking replication and DNA synthesis, but also by promoting apoptosis [51, 52]. It seems that MCM10 can be a good target for therapy in both UTUC and UBUC [53].

Sulfatase-1

Human sulfatase-1 (SULF-1) controls the sulfation status of heparan sulphate proteoglycan and can be up- or down-regulated promoting or inhibiting tumour development [54]. SULF-1 downregulates multiple pathways in heparan sulphate binding growth factors like HGF, FGF2, VEGF, PDGF displaying suppressing function in multiple cancers (hepatocellular carcinoma, ovarian cancer, renal and multiple myeloma) [55]. However, it seems that increased expression of SULF-1 in other cancers like breast, lung, gastric cancers, glioma and leukaemia promote tumorigenesis [56,57]. High expression of SULF-1 is correlated with poor prognostic and metastatic risk in patients with UBUC or UTUC. This correlation is also proportional to the tumour grade, nodal involvement and vascular invasion. Exogenous wild type SULF-1 is involved in tumour migration and invasion through Akt phosphorylation but also other pathway activation. SULF-1 plays a critical role in the development of UC, and can be an important therapeutic and prognostic factor [58].

III. CONCLUSIONS

UTUC and UBUC are to cancer types with many similarities but also important differences. In these two cancer types, many times, the therapeutic approach is different because the prognostic is different. The aggressivity and poor prognostic in UTUC make therapeutic strategies difficult. We need a better understanding of the molecular processes underlying these tumours. We need more reliable prognostic and therapeutic factors in order to use targeted drugs in the aim of improving the patient's outcome and overall survival.

ACKNOWLEDGMENT

The authors thank to the staff of Victor Babeș University of Medicine and Pharmacy, Timisoara, for the opportunity created in conducting this review, and also for the entire support of the colleagues from the Department of Histology, Angiogenesis Research Center Timisoara.

Declaration of conflict of interests: The authors declare no conflict of interest regarding the publication of this article.

REFERENCES

[1] Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, Cowan NC, Gontero P, Van Rhijn BWG, Mostafid AH, Palou J, Shariat SF. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol. 2018;73(1):111-122.

[2] Gandaglia G, Bianchi M, Trinh QD, Becker A, Larouche A, Abdollah F, Roghmann F, Tian Z, Shariat SF, Briganti A, Montorsi F, Karakiewicz PI, Sun M. Survival after nephroureterectomy for upper tract urothelial carcinoma: a population-based competing-risks analysis. Int J Urol. 2014;21(3):249-256.

[3] Moussa S, Yafi FA, El-Hakim A, Fahmy N, Aprikian A, Tanguay S, Anidjar M, Kassouf W. Outcome of surgical treatment of patients with upper versus lower urinary tract urothelial carcinoma: stage-by-stage comparison. Urol Int. 2010;84(1):50-55.

[4] Stewart GD, Bariol SV, Grigor KM, Tolley DA, McNeill SA. A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract. BJU Int. 2005;95(6):791-793.

[5] Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, Hinoue T, Laird PW, Hoadley KA, Akbani R, Castro MAA, Gibb EA, Kanchi RS, Gordenin DA, Shukla SA, Sanchez-Vega F, Hansel DE, Czerniak BA, Reuter VE, Su X, de Sa Carvalho B, Chagas VS, Mungall KL, Sadeghi S, Pedamallu CS, Lu Y, Klimczak LJ, Zhang J, Choo C, Ojesina AI, Bullman S, Leraas KM, Lichtenberg TM, Wu CJ, Schultz N, Getz G, Meyerson M, Mills GB, McConkey DJ; TCGA Research Network, Weinstein JN, Kwiatkowski DJ, Lerner SP. Comprehensive

Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell. 2017;171(3):540-556.e25.

[6] Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, Roth B, Cheng T, Tran M, Lee IL, Melquist J, Bondaruk J, Majewski T, Zhang S, Pretzsch S, Baggerly K, Siefker-Radtke A, Czerniak B, Dinney CP, McConkey DJ. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014;25(2):152-165.

[7] Donin NM, Lenis AT, Holden S, Drakaki A, Pantuck A, Belldegrun A, Chamie K. Immunotherapy for the Treatment of Urothelial Carcinoma. J Urol. 2017;197(1):14-22.

[8] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909-1920.

[9] Sfakianos JP, Cha EK, Iyer G, Scott SN, Zabor EC, Shah RH, Ren Q, Bagrodia A, Kim PH, Hakimi AA, Ostrovnaya I, Ramirez R, Hanrahan AJ, Desai NB, Sun A, Pinciroli P, Rosenberg JE, Dalbagni G, Schultz N, Bajorin DF, Reuter VE, Berger MF, Bochner BH, Al-Ahmadie HA, Solit DB, Coleman JA. Genomic Characterization of Upper Tract Urothelial Carcinoma. Eur Urol. 2015;68(6):970-977.

[10] Wu S, Chen J, Dong P, Zhang S, He Y, Sun L, Zhu J, Cheng Y, Li X, Tang A, Huang Y, Gui Y, Liu C, Yang G, Zhou F, Cai Z, Wang R. Global gene expression profiling identifies ALDH2, CCNE1 and SMAD3 as potential prognostic markers in upper tract urothelial carcinoma. BMC Cancer. 2014;14:836.

[11] Ramji DP, Foka P. CCAAT/enhancer-binding proteins: structure, function and regulation. Biochem J. 2002;365(Pt 3):561-575.

[12] Agrawal S, Hofmann WK, Tidow N, Ehrich M, van den Boom D, Koschmieder S, Berdel WE, Serve H, Müller-Tidow C. The C/EBPdelta tumor suppressor is silenced by hypermethylation in acute myeloid leukemia. Blood. 2007;109(9):3895-3905.

[13] Hour TC, Lai YL, Kuan CI, Chou CK, Wang JM, Tu HY et al. Transcriptional up-regulation of SOD1 by CEBPD: A potential target for cisplatin resistant human urothelial carcinoma cells. Biochemical Pharmacology. 2010; 80:325- 334.

[14] Wang YH, Wu WJ, Wang WJ, Huang HY, Li WM, Yeh BW, Wu TF, Shiue YL, Sheu JJ, Wang JM, Li CF. CEBPD amplification and overexpression in urothelial carcinoma: a driver of tumor metastasis indicating adverse prognosis. Oncotarget. 2015;6(31):31069-31084.

[15] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014;507(7492):315-322.

[16] Bakkar AA, Wallerand H, Radvanyi F, Lahaye JB, Pissard S, Lecerf L, Kouyoumdjian JC, Abbou CC, Pairon JC, Jaurand MC, Thiery JP, Chopin DK, de Medina SG. FGFR3 and TP53 gene mutations define two distinct pathways in urothelial cell carcinoma of the bladder. Cancer Res. 2003;63(23):8108-8112.

[17] Millis SZ, Bryant D, Basu G, Bender R, Vranic S, Gatalica Z, Vogelzang NJ. Molecular profiling of infiltrating urothelial carcinoma of bladder and nonbladder origin. Clin Genitourin Cancer. 2015;13(1):e37-e49.

[18] Lee JY, Kim K, Sung HH, Jeon HG, Jeong BC, Seo SI, Jeon SS, Lee HM, Choi HY, Kwon GY, Kim KM, Lee J, Lim HY, Park SH. Molecular Characterization of Urothelial Carcinoma of the Bladder and Upper Urinary Tract. Transl Oncol. Transl Oncol. 2018;11(1):37-42.

[19] Tomlinson DC, Lamont FR, Shnyder SD, Knowles MA. Fibroblast growth factor receptor 1 promotes proliferation and survival via activation of the mitogen-activated protein kinase pathway in bladder cancer. Cancer Res. 2009;69(11):4613-4620.

[20] Blockus H, Chédotal A. Slit-Robo signaling. Development. 2016;143(17):3037-3044.

[21] Dickinson RE, Dallol A, Bieche I, Krex D, Morton D, Maher ER, Latif F. Epigenetic inactivation of SLIT3 and SLIT1 genes in human cancers. Br J Cancer. Br J Cancer. 2004;91(12):2071-2078.

[22] Bang C, Thum T. Exosomes: new players in cell-cell communication. Int J Biochem Cell Biol. 2012;44(11):2060-2064.

[23] Lodygin D, Tarasov V, Epanchintsev A, Berking C, Knyazeva T, Körner H, Knyazev P, Diebold J, Hermeking H. Inactivation of miR-34a by aberrant CpG methylation in multiple types of cancer. Cell Cycle. Cell Cycle. 2008;7(16):2591-2600.

[24] Andrew AS, Marsit CJ, Schned AR, Seigne JD, Kelsey KT, Moore JH, Perreard L, Karagas MR, Sempere LF. Expression of tumor suppressive microRNA-34a is associated with a reduced risk of bladder cancer recurrence. Int J Cancer. Int J Cancer. 2015;137(5):1158-1166.

[25] Li H, Yu G, Shi R, Lang B, Chen X, Xia D, Xiao H, Guo X, Guan W, Ye Z, Xiao W, Xu H. Cisplatin-induced epigenetic activation of miR-34a sensitizes bladder cancer cells to chemotherapy. Mol Cancer. 2014;13:8.

[26] Lee HY, Chen YJ, Li CC, Li WM, Hsu YL, Yeh HC, Ke HL, Huang CN, Li CF, Wu WJ, Kuo PL. Deduction of Novel Genes Potentially Involved in Upper Tract Urothelial Carcinoma Using Next-Generation Sequencing and Bioinformatics Approaches. Int J Med Sci. 2019;16(1):93-105.

[27] Wellenstein MD, de Visser KE. Cancer-Cell-Intrinsic Mechanisms Shaping the Tumor Immune Landscape. Immunity. 2018;48(3):399-416.

[28] Marzouka NA, Eriksson P, Rovira C, Liedberg F, Sjödahl G, Höglund M. A validation and extended description of the Lund taxonomy for urothelial carcinoma using the TCGA cohort. Sci Rep. 2018;8(1):3737.

[29] Tokarev A, Skasko M, Fitzpatrick K, Guatelli J. Antiviral activity of the interferon-induced cellular protein BST-2/tetherin. AIDS Res Hum Retroviruses. 2009;25(12):1197-1210.

[30] Krejci P, Prochazkova J, Bryja V, Jelinkova P, Pejchalova K, Kozubik A, Thompson LM, Wilcox WR. Fibroblast growth factor inhibits interferon gamma-STAT1 and interleukin 6-STAT3 signaling in chondrocytes. Cell Signal. 2009;21(1):151-160.

[31] Karkera JD, Cardona GM, Bell K, Gaffney D, Portale JC, Santiago-Walker A, Moy CH, King P, Sharp M, Bahleda R, Luo FR, Alvarez JD, Lorenzi MV, Platero SJ. Oncogenic Characterization and Pharmacologic Sensitivity of Activating Fibroblast Growth Factor Receptor (FGFR) Genetic Alterations to the Selective FGFR Inhibitor Erdafitinib. Mol Cancer Ther. 2017;16(8):1717-1726.

[32] Nogova L, Sequist LV, Perez Garcia JM, Andre F, Delord JP, Hidalgo M, Schellens JH, Cassier PA, Camidge DR, Schuler M, Vaishampayan U, Burris H, Tian GG, Campone M, Wainberg ZA, Lim WT, LoRusso P, Shapiro GI, Parker K, Chen X, Choudhury S, Ringeisen F, Graus-Porta D, Porter D, Isaacs R, Buettner R, Wolf J. Evaluation of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Kinase Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in Fibroblast Growth Factor Receptors: Results of a Global Phase I, Dose-Escalation and Dose-Expansion Study. J Clin Oncol. 2017;35(2):157-165.

[33] Robinson BD, Vlachostergios PJ, Bhinder B, Liu W, Li K, Moss TJ, Bareja R, Park K, Tavassoli P, Cyrta J, Tagawa ST, Nanus DM, Beltran H, Molina AM, Khani F, Miguel Mosquera J, Xylinas E, Shariat SF, Scherr DS, Rubin MA, Lerner SP, Matin SF, Elemento O, Faltas BM. Upper tract urothelial carcinoma has a luminal-papillary T-cell depleted contexture and activated FGFR3 signaling. Nat Commun. 2019;10(1):2977.

[34] Carl-McGrath S, Lendeckel U, Ebert M, Röcken C. Ectopeptidases in tumour biology: a review. Histol Histopathol. 2006;21(12):1339-1353.

[35] Sevenich L, Joyce JA. Pericellular proteolysis in cancer. Genes Dev. 2014;28(21):2331-2347.

[36] Kikkawa F, Kajiyama H, Shibata K, Ino K, Nomura S, Mizutani S. Dipeptidyl peptidase IV in tumor progression. Biochim Biophys Acta. 2005;1751(1):45-51.

[37] Iwata S, Morimoto C. CD26/dipeptidyl peptidase IV in context. The different roles of a multifunctional ectoenzyme in malignant transformation. J Exp Med. 1999;190(3):301-306.

[38] Choi HJ, Kim JY, Lim SC, Kim G, Yun HJ, Choi HS. Dipeptidyl peptidase 4 promotes epithelial cell transformation and breast tumourigenesis via induction of PIN1 gene expression. Br J Pharmacol. 2015;172(21):5096-5109.

[39] Cheng HC, Abdel-Ghany M, Pauli BU. A novel consensus motif in fibronectin mediates dipeptidyl peptidase IV adhesion and metastasis. J Biol Chem. 2003;278(27):24600-24607.

[40] Gorrell MD, Gysbers V, McCaughan GW. CD26: a multifunctional integral membrane and secreted protein of activated lymphocytes. Scand J Immunol. 2001;54(3):249-264.

[41] Aoe K, Amatya VJ, Fujimoto N, Ohnuma K, Hosono O, Hiraki A, Fujii M, Yamada T, Dang NH, Takeshima Y, Inai K, Kishimoto T, Morimoto C. CD26 overexpression is associated with prolonged survival and enhanced chemosensitivity in malignant pleural mesothelioma. Clin Cancer Res. 2012;18(5):1447-1456

[42] Cordero OJ, Salgado FJ, Nogueira M. On the origin of serum CD26 and its altered concentration in cancer patients. Cancer Immunol Immunother. 2009;58(11):1723-1747.

[43] Barreira da Silva R, Laird ME, Yatim N, Fiette L, Ingersoll MA, Albert ML. Dipeptidylpeptidase 4 inhibition enhances lymphocyte trafficking, improving both naturally occurring tumor immunity and immunotherapy. Nat Immunol. 2015;16(8):850-858.

[44] Liang PI, Yeh BW, Li WM, Chan TC, Chang IW, Huang CN, Li CC, Ke HL, Yeh HC, Wu WJ, Li CF. DPP4/CD26 overexpression in urothelial carcinoma confers an independent prognostic impact and correlates with intrinsic biological aggressiveness. Oncotarget. 2017;8(2):2995-3008.

[45] Homesley L, Lei M, Kawasaki Y, Sawyer S, Christensen T, Tye BK. Mcm10 and the MCM2-7 complex interact to initiate DNA synthesis and to release replication factors from origins. Genes Dev. 2000;14(8):913-926.

[46] Lee JK, Seo YS, Hurwitz J. The Cdc23 (Mcm10) protein is required for the phosphorylation of minichromosome maintenance complex by the Dfp1-Hsk1 kinase. Proc Natl Acad Sci U S A. 2003;100(5):2334-2339.

[47] Kliszczak M, Sedlackova H, Pitchai GP, Streicher WW, Krejci L, Hickson ID. Interaction of RECQ4 and MCM10 is important for efficient DNA replication origin firing in human cells. Oncotarget. 2015;6(38):40464-40479.

[48] Wohlschlegel JA, Dhar SK, Prokhorova TA, Dutta A, Walter JC. Xenopus Mcm10 binds to origins of DNA replication after Mcm2-7 and stimulates origin binding of Cdc45. Mol Cell. 2002;9(2):233-240.

[49] Watase G, Takisawa H, Kanemaki MT. Mcm10 plays a role in functioning of the eukaryotic replicative DNA helicase, Cdc45-Mcm-GINS. Curr Biol. 2012;22(4):343-349.

[50] Jones RM, Petermann E. Replication fork dynamics and the DNA damage response. Biochem J. 2012;443(1):13-26.

[51] Shreeram S, Sparks A, Lane DP, Blow JJ. Cell type-specific responses of human cells to inhibition of replication licensing. Oncogene. 2002;21(43):6624-6632.

[52] Going JJ, Keith WN, Neilson L, Stoeber K, Stuart RC, Williams GH. Aberrant expression of minichromosome maintenance proteins 2 and 5, and Ki-67 in dysplastic squamous oesophageal epithelium and Barrett's mucosa. Gut. 2002;50(3):373-377.

[53] Li WM, Huang CN, Ke HL, Li CC, Wei YC, Yeh HC, Chang LL, Huang CH, Liang PI, Yeh BW, Chan TC, Li CF, Wu WJ. MCM10 overexpression implicates adverse prognosis in urothelial carcinoma. Oncotarget. 2016;7(47):77777-77792.

[54] Morimoto-Tomita M, Uchimura K, Werb Z, Hemmerich S, Rosen SD. Cloning and characterization of two extracellular heparin-degrading endosulfatases in mice and humans. J Biol Chem. 2002;277(51):49175-49185.

[55] Narita K, Staub J, Chien J, Meyer K, Bauer M, Friedl A, Ramakrishnan S, Shridhar V. HSulf-1 inhibits angiogenesis and tumorigenesis in vivo. Cancer Res. 2006;66(12):6025-6032.

[56] Bret C, Moreaux J, Schved JF, Hose D, Klein B. SULFs in human neoplasia: implication as progression and prognosis factors. J Transl Med. 2011;9:72.

[57] Rosen SD, Lemjabbar-Alaoui H. Sulf-2: an extracellular modulator of cell signaling and a cancer target candidate. Expert Opin Ther Targets. 2010;14(9):935-949.

[58] Lee HY, Yeh BW, Chan TC, Yang KF, Li WM, Huang CN, Ke HL, Li CC, Yeh HC, Liang PI, Shiue YL, Wu WJ, Li CF. Sulfatase-1 overexpression indicates poor prognosis in urothelial carcinoma of the urinary bladder and upper tract. Oncotarget. 2017;8(29):47216-47229.