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Review

Understanding the biology of urothelial cancer metastasis

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Abstract Management of unresectable urothelial cancer (UC) has been a clinical challenge for decades. While drug resistance is a key issue, precise understanding of biology of UC metastasis is another challenge for the improvement of treatment outcome of UC patients. Introduction of the cell biology concepts including epithelial-mesenchymal transition (EMT) and cancer stemness seems to explain UC metastasis. Molecular genetics based on gene expression profiling, next generation sequencing, and explosion of non-coding RNA world has opened the door to intrinsic molecular subtyping of UC. Next steps include, based on the recently accumulated understanding, the establishment of novel disease models representing UC metastasis in various experimental platforms, particularly *in vivo* animal systems. Indeed, novel knowledge molecular genetics has not been fully linked to the modeling of UC metastasis. Further understanding of bladder carcinogenesis is needed particularly with regard to cell of origin related to tumor characteristics including driver gene alterations, pathological differentiations, and metastatic ability. Then we will be able to establish better disease models, which will consequently lead us to further understanding of biology and eventually the development of novel therapeutic strategies for UC metastasis.
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1. Introduction

Bladder cancer is the sixth most common malignancy excluding non-melanoma skin cancers with an estimation of 330,380 new cases and 123,051 deaths from bladder cancer worldwide in 2012 [1]. Approximately 95% of bladder cancers are histologically classified as urothelial carcinoma (hereafter referred as UC, formerly called transitional cell carcinoma) with the exception of a particular area where squamous cell carcinoma due to chronic infection of *Schistosoma hematobium*is more prevalent. Urothelium, where UC is originated, lines all through the urinary tract

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except for distal urethra. Therefore, UC can arise from renal pelvis, ureter, bladder, and proximal urethra.

As many of other malignancies, bladder UC is a disease of older individuals. Patients are typically in their fifth or greater decades of life. The majority of bladder UC occur in males where there is an approximately 2- to 3-fold greater incidence compared with females. In the United States, Caucasians are at highest risk for bladder UC among all races including African, Asian, and Latin Americans. It is known that smoking and occupational or endemic exposures to certain chemicals predispose us to UC. The underlying mechanisms that link urothelial carcinogenesis to the sexual and racial disparities and risk factors including aging and carcinogens are currently not fully understood.

Treatment and prognosis of UC depend on several key factors including anatomical site, extent (stage), and histological grade of the disease. Non-muscle-invasive bladder UC (NMIBC),with the exception of carcinoma *in situ* (CIS), can be treated by transurethral resection with excellent survival outcomes, whereas muscle-invasive bladder UC (MIBC) and upper urinary tract UC (UTUC) often need radical cystectomy (RC) or nephroureterectomy (RNU). While these treatments are usually indicated with a curative intent, there are currently few curative treatment options for a metastatic or recurrent UC that has progressed outside of the urinary tract. MIBC is associated with higher incidence of distant metastasis compared with NMIBC. Bladder UC often metastasize to lymph nodes, bone, lung, liver, and peritoneum [2]. Systemic chemotherapy, the standard treatment for metastatic UC, can hardly achieve durable disease control. Therefore, treatment outcome of the patients with metastatic UC has been very poor with approximately 15% of overall survival rate [3].

Thus, it is apparently important to understand the underlying biology for metastatic progression of UC. Recently published series of molecular genetics of bladder cancer provided novel information for intrinsic molecular subtyping of UC [4–6], which will potentially lead us to the effective prevention and cure of this currently lethal form of the disease. This article reviews recent key findings that have been accumulated in the research field of UC metastasis, barriers that hamper our research progression, and future perspectives that may potentially overcome them.

2. Cell biology of UC metastasis

2.1. Epithelial-mesenchymal transition (EMT)

Several cellular processes are implicated in metastatic progression of UC. EMT is referred as a complex process that reprograms and transmogrifies epithelial cells to mesenchymal phenotype characterized by loss of cell adhesion and polarity. Although EMT is a phenomenon that physiologically observed during development and wound healing, it has long been implicated in cancer metastasis and treatment resistance. As essential roles of EMT in urothelial cancer metastasis was extensively discussed in an excellent review by McConkey et al. [7] in 2009, this article focuses on relatively recent findings.

One of the most particular molecular characteristics of cells undergoing EMT is downregulation of surface CDH-1 (cadherin 1, also known as E-cadherin) and EMT is best characterized by decreased expression of CDH-1 and increased expression of CDH-2 (N-cadherin). Indeed, aberrantly attenuated expression of CDH-1 was reported to be associated with high progression rate of bladder UC [8,9]. Recently Al-Ahmadie et al. [10] observed truncating somatic mutations in the *CDH-1* gene in 84% of plasmacytoid bladder cancers, a highly invasive histological variant of UC. Knock-out of CDH-1 in bladder UC cells enhanced cell migration, suggesting that loss of CDH-1 expression is not just a marker for EMT, but has some central, causal, and functional significance in tumor invasion and progression.

It is well known that numerous signaling pathways involving TGFβ, integrins, Notch, Wnt, and sonic hedgehog (SHH) induce EMT [7,11]. Recent studies addressed molecular mechanisms involved in TGFβ-induced EMT in UC cells. Those studies revealed malat-1 [12,13] and EIF5A2 [14] downstream mediators of TGFβ signaling pathway that induce EMT. Another study showed that PPM1A functions as a negative regulator of EMT by dephosphorylating TGFβ-activated Smad2/3 [15]. Although those reports suggest that TGFβ signaling promotes EMT in UC, another study showed that GDF15, a member of TGFβ superfamily, inhibits EMT through upregulating mammary serine protease inhibitor (MASPIN) and N-myc downstream-regulated family genes (*NDRG1*, *NDRG2*, and *NDRG3*) [16]. Additionally, it is yet to be fully understood what cellular interaction including auto- and para-crine mechanisms induce TGFβ signaling in the microenvironment of UC tumors.

Several recent reports suggested that integrins and associated signaling pathways are implicated in EMT of UC. Integrins mediate cellular adhesion to extracellular matrix (ECM). In the process of EMT, coordinated regulation of the integrin-mediated cell–ECM adhesion and E-cadherin-mediated cell–cell adhesion is required [17]. A report showed that knockdown of αv integrinsled UC cells to a shift towards more epithelial track characterized by increased CDH-1/CDH-2 ratio and downregulation of EMT-associated genes including *SNAI2*, *NANOG*, *BMI1*, *ALDH1* [18]. Importantly, these phenotypic changes were associated with decreased metastatic growth ability of the cells. Integrin-linked kinase (ILK) is highly evolutionally conserved serine/threonine kinase binding to β1 integrin [19]. Like other focal adhesion molecules such as c-Src and FAK, it mediates outside-inside signal transduction from ECM–integrin interaction. It was reported that ILK expression is higher in mesenchymal UC cells compared with epithelial ones [20]. Exogenous expression of ILK led epithelial UC cells to mesenchymal shift through activation of GSK3β–Zeb1 pathway. Importantly, ILK expression is positively correlated with invasive phenotype of human and murine bladder UC. These findings indicate that ECM–integrin adhesion plays a key role for cancer cell plasticity as well as E-cadherin-mediated cell–cell adhesion.

When we consider that EMT occurs physiologically during embryonic development and tissue repair, it is not surprising that EMT in cancer cells are also regulated by the developmental signaling pathways including SHH, Wnt, and Notch pathways. Specifically, recent studies have shed light on the role of SHH signaling in urothelium and UC. Beachy's group found that basal urothelial cells expressing SHH gave a rise of whole urothelial layer [21]. They also

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