Seminars in Cancer Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Genito-urinary genomics and emerging biomarkers for immunomodulatory cancer treatment

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ARTICLE INFO

Keywords:
Immunotherapy
Bladder
Kidney
Prostate
Biomarkers

ABSTRACT

Immunotherapy is gradually becoming a key factor in the therapeutic algorithm for patients with genito-urinary (GU) cancers at different stages of disease. Robust and reliable biomarkers are crucial for an appropriate inclusion of patients in clinical trials and for a reliable patient selection for treatments with immunomodulatory drugs. The increasing knowledge on the genomic landscape of GU cancers supports stratification of patients for targeted therapies. This review focusses on emerging biomarkers and the role of genomics in predicting clinical benefit to immunomodulatory agents in GU cancers. Based on cancer incidences and available data we restricted this overview to bladder, prostate and renal cancer.

1. Introduction

The exponential increase in knowledge on cancer genomics is changing the diagnostic and therapeutic approach of genito-urinary (GU) cancers. It gradually becomes clear that the genomic signatures of individual cancers may account for different prognosis and therapeutic decisions. Although clinically available targeted therapies based on genomic alterations in GU cancers are still limited, more insight is being gained in the different genomic subgroups per cancer type and this knowledge is likely to lead us to clinically prognostic and therapeutic relevance.

Immunotherapy is an upcoming and promising approach in the treatment of GU malignancies and several immunotherapeutic drugs have been approved by the Food and Drug Administration (FDA) and European Commission recently [1]. The availability of reliable biomarkers for immunomodulatory drugs is crucial to get an optimal patient selection, to limit drug-related side-effects [2] and to gain cost-efficiency [3].

An intriguing field related to cancer genomics and immunotherapy is the relationship among the genomic landscape of the tumour, mutational load, and benefit from treatment. It has been shown that the genomic landscape of a tumour affects the clinical benefit provided by immunomodulatory agents [4,5], and several possible underlying mechanisms, such as the role of neoantigen load in driving T cell responses [6], the presence of mutant tumour antigen-specific T cells [7], the association between somatic mutations associated with immune infiltrates [8] and tumour-intrinsic resistance to cytolytic activity have been elucidated [9].

In this review, we tried to give an overview of recent evolutions in GU cancer genomics and immunomodulatory therapies, with a focus on emerging biomarkers and the role of genomics in predicting clinical benefit to immunomodulatory agents. We think that in this context it is

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http://dx.doi.org/10.1016/j.semcancer.2017.10.004
Received 15 June 2017; Received in revised form 4 October 2017; Accepted 6 October 2017

essential to define the concepts 'prognostic' and 'predictive' biomarkers. A prognostic biomarker informs about a likely cancer outcome (e.g., disease recurrence, disease progression, death) independent of treatment received, while a biomarker is predictive if the treatment effect (experimental compared with control) is different for biomarker-positive patients compared with biomarker-negative patients [10]. Biomarkers cover a range of possible biologic entities. In this review, we have tried to focus most on tissue-based biomarkers, ranging from protein to genomic level. Blood-based biomarkers, like immune cell ratios, cell-free DNA… are only briefly discussed. Based on cancer incidences and available data we restricted this overview to bladder, prostate and renal cancer.

2. Urothelial carcinoma

Bladder cancer (BC) is the ninth most common cancer worldwide [11,12]. Histopathology is still the mainstay in diagnosis, but in recent years, literature has shown evidence for the existence of several subtypes based on molecular characteristics. The classic histopathological distinction between non-muscle-invasive BC (NMIBC – pTa, pT1, carcinoma in situ [CIS]) and muscle-invasive BC (MIBC – ≥pT2) is reflected by parallel genomic subgroups. Earlier work showed that urothelial carcinomas (UC) arise and progress along two different pathways [13–16]. The majority of UC (70–80%) are low-grade papillary NMBIC, and harbour frequent mutations in the HRAS and FGFR3 genes [13–16]. The minor part of UC are characterised as high grade invasive tumours, which either originate from flat CIS or from progression in the low-grade pathway, and with the presence of frequent alterations in the tumour suppressor TP53, retinoblastoma (RB) and gene cyclin-dependent kinase inhibitor 2A (CDKN2A) genes [13–16].

Most of genomic studies have focused on MIBC. Comprehensive classification schemes for MIBC have been proposed by separate groups, at Lund University (Lund) [17], MD Anderson (MDA) [18], University of North Caroline (UNC) [19] and the Cancer Genome Atlas Project Consortium (TCGA) [20]. Several differences are present between the individual classification systems, based on cohort stage composition and basic questions posed by the respective investigators, but recent work has shown considerable overlap between the different classifiers [21–23]. At present we can distinguish 2 main subgroups in MIBC: basal and luminal tumours [17–19,22,24]. The basal or squamous-like subgroup (TCGA cluster III) is characterised by overexpression of basal markers such as K5 and K14 and downregulation of urothelial differentiation markers e.g. K20 and FOXA1 [19,20,22,25]. Another basal subgroup is the claudin-low subtype (TCGA cluster IV) characterized by epithelial-to-mesenchymal (EMT) transition [17,19,20,22,26]. The luminal MIBC group can be divided in 2 subgroups: urothelial-like UC (TCGA cluster I) and genomic unstable/infiltrated/p53-like UC (TCGA cluster II) [17,19,20,22]. Urothelial-like UC are characterised by urothelial differentiation and harbour alterations in the FGFR3-pathway [17,19,20,22]. The genomic unstable (GU) group has expression of urothelial differentiation markers, amplification of PPARG, GATA-3 and ERBB2, but is not related to the FGFR3-pathway [17,19–22]. A recent update of the TCGA subtypes resulted in a luminal group, a luminal immune group, a basal group and an immune undifferentiated group [27]. Both immune-related groups were characterised by high expression of immune genes and variable expression of EMT-genes [27]. In general, basal subtypes have the worst prognosis but a better response to neo-adjuvant chemotherapy (NAC), whereas the genomic unstable or p53-like UC are more chemo-resistant [28,29]. The MDA group showed that immunohistochemical expressions of only two markers, luminal (GATA3) and basal (KRT5/6), were sufficient to identify the molecular subtypes of UC with over 90% accuracy [30]. On a recent consensus-meeting on molecular taxonomy for UC, the attendees found a robust consensus on 2 different molecular subtypes: a basal/squamous-like subgroup (proposed acronym: BASQ) to designate the tumours displaying the KRT5/6$^+$ KRT14$^+$ FOXA1$^-$ GATA3$^-$

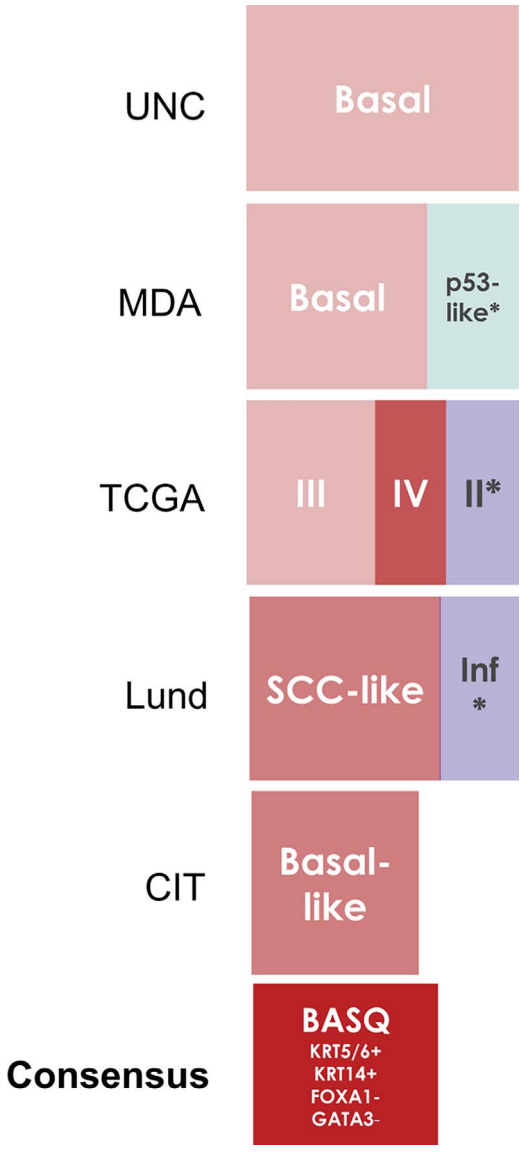

Fig. 1. Comparison of the proposed UC molecular classifications as they relate to the Basal-Squamous-like (BASQ) consensus group. The subtypes labelled with red background are overlapping among classifications, and comprise tumors that will be assigned to the BASQ subtype. Tumor subclasses in other colours (p53-like, TCGA, II, Infiltrated) comprise tumours that also express markers typical of urothelial differentiation to a variable extent. In red, the consensus definition of the BASQ subtype. Adapted with permission from reference [32].

phenotype and a differentiated subgroup correlating with the urobasal A tumours from the Lund classification [31,32] (see also Fig. 1). It was concluded that for the other subtypes more integrated work is needed to determine and validate their robustness [31,32]. Interestingly, similar subclassifications of NMIBC into three major classes with basal- and luminal-like characteristics and different clinical outcomes have recently been reported [33].

The presence of UC in Lynch syndrome (LS), a common genetic disease previously known as hereditary nonpolyposis colorectal cancer (HNPCC), has been largely underappreciated [34]. LS is a cancer-predisposing syndrome characterised by the autosomal dominant inheritance of a heterozygous germline mutation in one of the mismatch repair (MMR) genes [35]. Patients with LS are at increased lifetime risk to develop UC of the upper urinary tract [36,37] and the bladder [38]. UC in patients with LS are predominantly linked to MSH2 mutations [38–40]. Optimal screening for upper tract UC is still under debate and recommendations range from minimal to extensive surveillance [41]. A