ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 243–251

UROLOGIC ONCOLOGY

Seminar article

Biomarkers of renal cell carcinoma

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Received 10 April 2013; received in revised form 15 July 2013; accepted 17 July 2013

Abstract

The incidence of renal cell carcinoma (RCC) has increased steadily in past few decades and is partially attributable to the increased utilization of cross-sectional imaging. Many of these carcinomas are small incidental discoveries, although a subset leads to locally advanced or distant disease. Although its molecular pathophysiology is not completely understood, knowledge of hereditary RCCs has shed light on some of the pathways involved. More recently, the rapid advances in genomics, proteomics, and metabolomics have allowed for a deeper and more nuanced understanding of the genetic aberrations that lead up to and result from the transformation of a renal tubular epithelial cell into a carcinoma. These discoveries have allowed for the development of novel therapeutics that target these pathways. They have also led to the development of diagnostic, prognostic, and predictive biomarkers that could radically change the way RCC is diagnosed and treated. Although some of the current investigations are nascent and it remains to be seen which biomarkers will become clinically available, many candidate biomarkers show promise and require external validation. Ultimately, biomarkers may allow for cost-effective screening of high-risk patients, the identification of aggressive cancers among small renal masses, the identification of high-risk patients, the detection of recurrences postoperatively with minimal imaging, and the ability to choose appropriate targeted therapies for patients with metastatic disease.

Keywords: Renal cell carcinoma; Biomarkers; Diagnostic; Prognostic; Predictive

Introduction

In the United States, the incidence of renal cell carcinoma (RCC) has increased between 2% and 4% annually in the past few decades, a trend that is at least partially attributable to the rising utilization of cross-sectional imaging leading to incidental diagnosis of asymptomatic lesions [1]. In 2013, cancers of the kidney will account for an estimated 65,150 new cases and 13,680 deaths [2]. RCCs include several histological subtypes such as clear cell (80%), papillary (10%), chromophobe (5%), and medullary and collecting duct (<1%), whereas unclassified subtypes account for less than 5% of all RCCs [3]. It is believed that clear cell and papillary RCCs arise from the proximal tubules, whereas chromophobe RCC arises from the distal nephron and collecting duct carcinoma arises from the ducts of Bellini [4–6].

The exact etiology of RCC is unclear and probably multifactorial, although smoking, obesity, and hypertension have been identified as risk factors [7]. A small percentage of RCCs result from hereditary abnormalities and have allowed for detailed studies in the metabolic derangements that underlie the pathogenesis of these cancers, the most common one being the von Hippel-Lindau (VHL) tumor suppressor pathway in clear cell RCC [8]. This has led to a greater understanding of the molecular basis of this disease and the identification of potential biomarkers [9].

To address the rapid expansion of knowledge in the molecular basis of disease, the National Institutes of Health (NIH) convened a working group of experts to define standard terms, definitions, and a conceptual model for biomarker research. Biomarkers as defined by the NIH Biomarkers Definitions Working Group have several important clinical applications including the diagnosis, prognostication, and prediction and monitoring response to therapy [10]. In the realm of urologic oncology, prostate-specific antigen has served all of these roles since its introduction and dissemination [11,12]. Since the first study looking for a biomarker for RCC in the 1970s [13], there has been rapid expansion in translational research studying biomarkers for RCC in recent years owing to improved methods in high-throughput genomics, proteomics, and metabolomics. In this study, we systematically reviewed the literature on

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1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2013.07.011

biomarkers for RCC and examined their uses through the framework provided by the NIH Biomarkers Working Group.

Methods

We queried PubMed with the search phrase "renal cell carcinoma and biomarker" and found 3,130 papers. This initial search was then limited to papers in English and those to which we had access to the full-text article, narrowing down the results to 2,457 papers. The abstract of each paper was reviewed and relevant papers were selected for inclusion.

Molecular basis of RCC

Most of the research in the molecular biology of RCC has focused on clear cell variant, the predominant subtype. Many investigators believe that one of the earliest events in the development of RCC is the inactivation of the VHL tumor suppressor gene on chromosome 3p because of the following reasons: (1) it is the predisposing genetic defect in patients with VHL syndrome who develop hereditary clear cell RCC, (2) it is the most common genetic aberration in sporadic clear cell RCC, and (3) it can be found in even the smallest and presumably earliest tumors [14].

Patients with VHL syndrome develop multiple bilateral RCCs in middle age, typically with loss of the second allele through deletion of the gene or inactivation of its promoter regions [15]. In patients with sporadic RCC, two-thirds have biallelic loss of VHL either by point mutation or by promoter hypermethylation [16]. The VHL gene product forms an E3 ubiquitin complex that targets proteins for degradation, the best understood of which is hypoxia-inducible factor 1-alpha (HIF-1α). Once unbound, HIF-1α dimerizes with HIF-1β and this complex modulates multiple downstream pathways responsible for the hypoxia response including angiogenesis, cell cycle regulation, apoptosis, and cell-matrix interactions [17]. Therefore, inactivation of the VHL gene results in the constitutive activation of HIF-1α and consequently the tissue hypoxia pathway in nonhypoxic conditions [18]. This leads to the overexpression of genes involved in the hypoxia response including vascular endothelial growth factor (VEGF), among many others [18]. The discovery of this pathway was the rationale for the use of tyrosine kinase inhibitors for the treatment of RCC. The role of other upstream regulators such as the mammalian target of rapamycin and downstream effectors, such as VEGF and platelet-derived growth factor, in the development and progression of RCC is under active research [17]. Despite all these advances, the exact mechanism by which a renal tubular epithelial cell that overexpresses hypoxia-induced genes transforms into a RCC is still undefined.

Biomarker source

Because biomarkers exist in various concentrations within a tumor cell, the tumor's local environment and the patient's body fluids, the source of the sample used in assays is important. Although tissue from the tumor itself is closest to the source, tumor heterogeneity may be a limiting factor. Recent work has shown that the genetic makeup of RCCs varies widely within a given tumor. Using exome sequencing and chromosomal analysis on spatially separated samples, investigators showed that for any given tumor, approximately two-thirds of the somatic mutations discovered were not found in every region sampled. There was also significant variation in the number and types of mutations and ploidy status in different regions of a single tumor [19]. Furthermore, an invasive procedure such as a biopsy or an extirpative operation with the potential for complications is required to obtain a sample. In contrast, body fluids such as blood are less labor intensive and less invasive to obtain, but distance from the site of cancer may attenuate the signal and introduce noise into assays [20]. Biomarkers in the blood, for example, are susceptible to degradation by circulating proteases and nucleases, thereby dampening their signal [21]. Conversely, endogenous production of biomarker molecules by normal cells may artificially augment signals [22]. Urine metabolomic analysis is theoretically promising but difficulties with the heterogeneous nature of urine metabolites, potential contamination of nonhuman metabolites from genitourinary flora, and special handling requirements have limited the progress [23]. Recently, α-ketoglutarate, quinolinate, and nuclear matrix protein 2 have been identified as putative markers for early detection but much of this work is preliminary and requires further study [23,24]. At present, no standard approaches to biomarker sampling or analysis have been adopted for RCC as many of the putative tumor markers themselves are still under active investigation.

Diagnostic biomarkers

Increasingly frequently, the diagnosis of RCC begins with the discovery of a solid renal mass on cross-sectional imaging during the workup for another complaint. The challenge in treating these patients is the knowledge that about 12% of enhancing renal masses could be benign. The probability of cancer is proportional to the size of the mass: 55.7% of lesions 1 cm or less and 93.7% of lesions 7 cm or greater harbor malignancy [25]. There is also a weak correlation between lesion size and the probability of clear cell RCC histology and pathologic grading. Studies attempting to use radiographic findings to predict pathologic outcomes have historically been small and retrospective, with limited clinical applicability [26,27].