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Invited critical review

Bladder cancer diagnosis and recurrence prognosis: Comparison of markers with emphasis on survivin

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Abstract

Expression of the anti-apoptotic protein survivin is hardly detectable or even absent in many differentiated adult tissues, but is upregulated in almost any type of cancer. Furthermore, high survivin mRNA or protein expression generally correlates with an adverse disease course. Both these important features of survivin expression have been investigated for diagnostic and prognostic purposes in many human cancers, including bladder cancer. In this review, the role of survivin in the detection of bladder tumors and the prediction of tumor recurrence in patients with superficial bladder cancer will be discussed and compared to that of other markers/tests. The most promising marker(s) will be outlined. Also, important requirements for a successful implementation of such markers in a hospital setting are discussed. Finally, future directions for the discovery of new diagnostic or prognostic candidate markers will be mentioned.

Keywords: Bladder cancer; Diagnosis; Recurrence prediction; Survivin

Contents

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1. Introduction

Bladder cancer is the second most important cancer arising in the genitourinary tract [1]. The most common form of bladder cancer is urothelial cell carcinoma (UCC), comprising approximately 95% of all bladder tumors. The gold standard for the detection of tumors in the bladder is cystoscopy, a relatively accurate but invasive technique. Most of the patients diagnosed with UCC have superficial tumors, of which the depth of invasion is limited to the (sub)mucosa of the bladder wall (stage Ta, T1). Superficial tumors can be removed relatively easy by transurethral resection (TURT). However, in about 70% of the patients, tumors recur after initial resection and some of these patients will eventually show progression towards invasive and more aggressive disease (stage T2-4). This necessitates frequent cystoscopic examination of all patients with superficial bladder cancer during follow-up, including those patients who remain recurrence-free for several years or even the rest of their lives after surgery. Therefore, both non-invasive detection of bladder cancer and accurate prediction of tumor recurrence may significantly reduce the number of (follow-up) cystoscopies and could individualize patient treatment.

Cystoscopy detects bladder tumors relatively accurately. It is, however, invasive and represents a high burden to the patient. Also, small papillary lesions and flat-growing carcinoma in situ (Cis) tumors are frequently missed [2–4]. Many research groups have, therefore, investigated possibilities of replacing cystoscopy with a more accurate non-invasive diagnostic test. Numerous alternatives have been put forward, but although many of the tests seem promising, none has proven to be a reliable replacement of cystoscopy yet.

Another focus in bladder cancer research is the prediction of tumor recurrence and tumor progression. This is generally determined by assessing pathological parameters like tumor stage and grade, tumor size, multiplicity and the presence of Cis in tumor biopsies removed during TURT. These parameters show reasonable predictive ability, but are observer-dependent. This necessitates the search for a more accurate and standardized test. The ability of molecular markers to predict tumor recurrence or progression has been investigated intensively over the last one and a half decades. Some studies have yielded interesting results that are worth validating in large patient cohorts. This could lead to the selection of a marker that may supplement or even replace the current prognostic standards. Thus far, no prognostic test has been implemented in a hospital setting yet.

In the ongoing search for new markers for the improvement of bladder cancer diagnosis and prognosis, the anti-apoptosis gene survivin has also been studied. Survivin was discovered at the end of the last century [5]. Expression of survivin is undetectable in terminally differentiated adult tissue, but is highly expressed in cancer tissue [5]. Generally, high survivin mRNA or protein expression is correlated with aggressive behavior of tumor cells and in many types of cancer, increased survivin levels are indicative of early disease relapse and short patient survival [6].

In the following section, a brief introduction about survivin protein structure, function and expression will be presented. Subsequently, the diagnostic potential of survivin in bladder cancer will be compared to that of other markers/tests. Here, the focus will be on urine-based tests for the diagnosis of primary or recurrent bladder cancer. Next, the prognostic potential of survivin mRNA and protein expression in tumor tissue, urinary cells, patient serum and bladder washes will be discussed. Thus far, survivin has been implicated mainly in the prediction of tumor recurrence in patients with superficial bladder cancer and not in the prediction of tumor progression. Therefore, we will only compare survivin to markers that are also involved in the prediction of tumor recurrence. Finally, some concluding remarks and future directions are mentioned.

2. Survivin

2.1. Structure and function

Survivin belongs to the family of inhibitor of apoptosis proteins (IAP). The protein contains one copy of the baculovirus IAP repeat (BIR) domain, a domain essential for apoptosis inhibition. At 16.5 kDa, survivin is the