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Role of bone morphogenetic proteins in transitional cell carcinoma cells

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Abstract

Bone morphogenetic proteins (BMPs) are pleiotropic growth factors that signal through an interaction with the membrane receptors—type-IA, -IB, and -II (BMP-RIA, -RIB, and -RII, respectively). Although the prototypical members of this group of growth factors were isolated as osteoinductive factors, recently accumulated data have suggested that these factors regulate malignant cells. Herein, we review the data concerning BMPs in transitional cell carcinoma cells.

Keywords: Bone morphogenetic proteins (BMPs); BMP receptor; Transitional cell carcinoma (TCC); Bladder TCC cell line

1. Introduction

Among urologic malignancies, transitional cell carcinoma of the urinary bladder is the second most frequently diagnosed one. In 2005, there will be an estimated 53,200 new cases and 12,200 deaths [1]. At initial presentation, superficial disease comprises 70–80% of cases, whereas the remaining 20–30% present with a muscle-invasive disease. As many as 50% of patients with a muscle-invasive disease have either a detectable or an occult metastatic disease at the time of diagnosis. Once diagnosed, superficial tumors (Ta and T1) are treated with a local resection while carcinoma in situ (Tis) usually requires an intravesical BCG therapy. Low grade papillary disease (Ta, T1) rarely progresses to muscle invasive disease; however, up to 30% of patients with Tis or high grade papillary tumor are refractory to intravesical therapy and progress to a more advanced disease [2]. For patients with a BCG-refractory Tis, intravesical therapy with valrubicin is an alternative [3]; however, as with muscle invasive disease radical cystectomy is the recommended treatment. Among patients undergoing a radical cystectomy, 14–33% of patients with a lymph node negative muscle-invasive disease will eventually die of their disease within 5 years of surgery. To optimize patient selection for available treatment options and to develop novel therapeutic strategies, additional information concerning the biology of bladder TCC cells is necessary. In this regard, BMPs are potent inhibitors of epithelial proliferation that potentially regulate cellular proliferation and metastasis of bladder TCC cells. In this review, we will highlight potential roles of BMPs in transitional cell carcinomas.

2. Molecular markers of TCC

Bladder TCC is classified as either superficial or invasive disease based on pathology and clinical behavior. Traditionally, tumor grade and stage have been the primary prognostic factor that influences

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treatment options and follow-up regimens. Nevertheless, there is a significant heterogeneity within the subgroups of TCC. Thus, molecular markers potentially can better predict the tumor behavior and lead to optimal treatment and follow-up for TCC patients. The molecular markers associated with bladder TCC can be classified broadly into three interrelated processes: (1) oncogenes; (2) tumor suppressors; and (3) regulators of metastasis. It is the accumulation of alteration of various genes, rather than a single genetic event, that determines the clinical behavior of TCC.

Oncogenes associated with bladder TCC include cH-*ras*, *c-myc*, and HER2/*neu*. Mutations of cH-ras have been correlated with prognosis of bladder TCC [4]; up to 20% of bladder TCC have alterations of codons 12 and 61 of *ras* oncogene [5,6]. Likewise, the overexpression of the *c-myc* oncogene has been suggested to play a role during bladder TCC progression [7]. However, more recent data have disputed the initial conclusion on the significance of c-myc expression in bladder TCC [8]. The HER2/*neu* oncogene encodes a transmembrane protein with tyrosine kinase activity similar to the epidermal growth factor receptor [9,10]. Multiple studies have suggested a close relationship between HER2/*neu* expression and tumor stage, tumor progression, metastasis, and overall survival [11–13]. Nevertheless, it has been reported that the status of HER2/*neu* is not an independent prognostic indicator in bladder TCC patients [13,14].

Most common tumor suppressors implicated in bladder TCC carcinogensis include those located on chromosome 9, 13, and 17. Of these, deletions of chromosome 9 are the most common chromosomal alterations detected in bladder TCC cells [15]. In fact, aberrant chromosome 9 is seen in both superficial and invasive bladder TCC, suggesting that the deletion of chromosome 9 is an early event during bladder TCC carcinogenesis. The majority of the changes on chromosome 9 are deletions of 9p21 locus which encompasses three potential tumor suppressor genes—$p16^{INK4A}$, $p14^{ARF}$, and $p15^{INK4B}$. Additional potential bladder TCC tumor suppressor gene candidates on chromosome 9 include TGF-β receptor type I located on locus 9q33–34 [16]. On chromosome 13, mutations of the retinoblastoma (RB) gene are found in up to 30% of bladder tumors [17,18] while p53 appears to be the important contributor to bladder TCC carcinogenesis on chromosome 17. Indeed, it has been reported that the increased p53 nuclear reactivity is associated with a poor prognosis in muscle invasive disease [19,20].

Metastatic regulators of bladder TCC reported to date involve either angiogenesis or degradation of extracellular matrix. Promoters of angiogenesis implicated in bladder TCC cells include basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). The urinary levels of both bFGF and VEGF have been reported to be higher in patients with bladder cancer [21,22]. On the other hand, the endogenous angiogenesis inhibitor thrombospondin-1 (TSP-1) has been shown to be down-regulated in muscle invasive bladder TCC cells [23]. Tumor induced degradation of extracellular matrix associated with bladder TCC cells include matrix metalloproteinases MMP-2 and -9. Elevated serum and urinary levels of these two matrix metalloproteinases have been found in patients with aggressive TCC [24].

3. BMPs: Biological functions and signaling

BMPs with more than 20 subtypes are the largest subfamily of the transforming growth factor-β (TGF-β) superfamily. They were initially characterized as factors that induce bone and cartilage formation [25,26]. Since then, it has been demonstrated that BMPs are critical during gastrulation, mesoderm formation, left–right symmetry, neural patterning, skeletal and limb development, organogenesis, gametogenesis, cellular chemotaxis, and cellular differentiation (reviewed in 27 and 28). More recent studies have demonstrated that BMPs play important role during hematopoiesis [29] and early thymocyte differentiation [30].

As with TGF-β, BMPs exist as a large dimeric proproteins in the cytoplasm and are cleaved by proteases during secretion. Once secreted, the mature 21–25 kDa dimeric ligand binds to membrane receptor on target cells. But prior to reaching the target cells, there appears to be another layer of regulator such as Noggin and Chordin in which these proteins either augment or attenuate movement and function of BMPs [31,32].

Once BMPs reach the receptors, its signaling follows the paradigm established by TGF-β signaling. BMP receptors are serine/threonine kinases and BMPs signal through an interaction with a heteromeric complex of BMP-RI and -RII [33]. Ligand binding results in a cross-phosphorylation of type I receptor by type II; type I receptor, in turn, interacts directly with the downstream signaling molecules, smads (reviewed in 34) (Fig. 1). Based on the elucidated functions, smads are divided into three classes: receptor activated smads (R-smads), common-mediator smads (Co-smads), and inhibitory smads (I-smads). With respect to BMP signaling, R-smads are 1, 5, and 8 while the I-smad is 6; only one Co-smad has been identified to