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p53 and chemosensitivity in bladder cancer

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Abstract Urothelial carcinoma is the second most common genitourinary malignancy. Although the majority of patients present with superficial bladder tumors, there are several clinical problems, such as progression to invasive tumors, poor prognosis of invasive tumors, and chemosensitivity. Alterations in p53 represent one of the most common genetic events in patients with invasive urothelial carcinoma and are suggested to be linked to tumor progression, prognosis, and chemosensitivity. p53 possesses various functions, including induction of cell-cycle arrest, apoptosis, DNA repair, and antioxidants; it acts as a killer and a healer. In this article, we review the roles of p53 pathways in bladder carcinogenesis and findings from recent studies of ours and other groups, and we discuss the clinical significance of the abrogation of p53 pathways in the treatment of urothelial carcinoma.

Key words Urothelial tumor · p53 · p21 · Molecular targeting therapy

Introduction

Urothelial tumor is a common malignancy of the genitourinary tract that arises from the renal pelvis and ureter as well as the urinary bladder.1 Histologically, transitional cell carcinomas (TCCs) are the most common subtypes and represent nearly 90% of all bladder cancers. Although the majority of patients present with superficial bladder tumors, 20% to 40% either present with or develop invasive disease. Once tumors become invasive, the long-term survival rate remains unsatisfactory. Approximately 50% of patients will relapse and die of cancer, even when they undergo complete and potentially curative surgery.2 Systemic chemotherapies including cisplatin, gemcitabine, or taxol are used for locally advanced disease or metastatic disease, but their response rates are approximately 50%–60%.3 To improve prognosis to develop a more sophisticated treatment strategy, the molecular mechanisms underlying the carcinogenesis of bladder cancer have been studied. The fruits of these enthusiastic studies have been applied to the development of molecular targets predicting prognosis, disease progression, and chemosensitivity, as well as targets for new treatment strategies.4

In these urothelial tumors, mutations in p53 are one of the most common genetic events. p53 is a well-characterized tumor suppressor gene, encoded by the TP53 gene located on chromosome 17p13.1. Mutations in p53 genes were suggested to be linked to tumor progression and prognosis.5,6 Furthermore, recent research has shed light on the various functions of wild-type p53 as well as the significance of mutations in p53: gain of function and heterogeneous functional loss of p53.7–9 For clinical use, several methods for the detection of mutations in p53 have been developed and applied in the clinical setting of various human malignant tumors, including urothelial tumors.10–12

In this article, we review the roles of p53 pathways in bladder carcinogenesis and findings from recent studies of ours and other groups, and we discuss the clinical significance of the abrogation of p53 pathways in the treatment of urothelial carcinoma.

The functions of wild-type p53 in apoptosis and cell survival

Although p53 was first thought to be an oncogene due to its overexpression in tumor cells, wild-type p53 is now believed to act as a tumor suppressor, and its functions are suppressed by loss of heterozygosity (LOH) and/or mutations.13 Wild-type p53 possesses various functions (Fig. 1). The best-established functions of p53 are the induction of growth arrest and apoptosis. Acute DNA damage triggers...
A rapid p53 response that inhibits phase-specific cell-cycle progression (G1-S) and mediates its control through the transcriptional activation of related genes. The status of post-translational modification of p53, and the presence of co-factors and other transcriptional factors have effects on the functions of p53.

**Fig. 1.** Biological functions of p53. p53 may induce cell-cycle arrest, apoptosis, and/or cell survival via the transcriptional activation of related genes. The status of post-translational modification of p53, and the presence of co-factors and other transcriptional factors have effects on the functions of p53.

**Fig. 2.** Methodology for detection of p53 alterations. Several methods have been used, including detection of loss of heterozygosity (LOH) in 17p13.1, mutation analysis, functional analysis using yeast cells, measurement of serum anti-p53 antibody (Ab), and immunohistochemistry (IHC). Single-strand conformational polymorphism (SSCP) and sequencing or DNA-array methods have been developed for mutation analysis. Ch, Chromosome; TA, transcriptional activity.

Excision repair (BER), homologous recombination (HR), and mismatch repair (MMR), although the precise mechanisms underlying the role of p53 in DNA repair have not been fully explored.17,18 p53 possesses an antioxidant function and protects the genome from oxidation by reactive oxygen species (ROS). *PIG1* (Galectin7), *SOD2*, and *GPX1* are also upregulated by p53 and can act as antioxidants.19-21 Sablina et al.22 showed that, in the absence of any genotoxic stress, the removal of p53 led to a rise in intracellular ROS associated with an increased mutation rate and chromosomal instability. Dietary supplementation with antioxidants such as N-acetylcysteine had a substantial effect on tumor incidence in *p53*−/− mice.

Thus, although acute DNA damage induces p53 and cell-cycle arrest, p53 acts as both as a killer and a healer, via the induction of apoptosis and DNA-repair/antioxidants, respectively.23 Determinants that define the fate of the cell are currently unknown and involve multiple parameters, including cell type, intensity of DNA damage, and the presence of cofactors such as p300, ASPP, or myc.24

### Significance of p53 alterations in bladder carcinogenesis

Based on numerous studies of the natural history of bladder tumors and the analysis of molecular events in superficial and invasive bladder cancers, two distinct pathways have been proposed to underlie bladder tumorigenesis.25,26 One is that low-grade superficial tumors are derived from normal urothelium via hyperplasia and the other is that normal urothelium develops into invasive tumors via dysplasia, high-grade pTa tumors, or carcinoma in situ. Key players in such bladder carcinogenesis have been identified by mutation analysis and loss of heterozygosity (LOH) analysis of bladder cancer tissues. LOH analysis and mutation analysis have revealed that the *HRAS* and *FGFR3* genes are associated with the generation of superficial papillary carcinomas, while alterations in *p53* and *retinoblastoma (Rb)* genes and pathways are associated with invasive bladder carcinomas.27

Generally, tumor suppressor genes and oncogenes are suppressed and activated by mutations involved in carcinogenesis. Although many tumor suppressor genes are functionally suppressed by truncating mutations, the majority of p53 mutations are missense substitutions (75%).28,29 Other alterations include frameshift insertions and deletions and other infrequent alterations.29 In particular, missense mutations were identified mainly in hotspots around the DNA-binding domain. Different forms of mutant p53 proteins are recognized to have different functional and biological effects, and these have been analyzed using functional assays in yeast and in human cells. Kato et al.30 have demonstrated, using yeast cells, that p53 with missense alterations generally shows a loss of transactivation activity on one or more p53-responsive elements (p53-REs), but some rare mutants retain significant transactivation activity.