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Minireview

The roles of p53R2 in cancer progression based on the new function of mutant p53 and cytoplasmic p21

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ABSTRACT

Although the deregulated expression of p53R2, a p53-inducible protein and homologue of the R2 subunit of ribonucleotide reductase, has been detected in several human cancers, p53R2 roles in cancer progression and malignancy still remains controversial. In this article, we present a viable hypothesis about the roles of p53R2 in cancer progression and therapy resistance based on the roles of cytoplasmic p21 and mutant p53. Since p53R2 can up-regulate p21 and p21, it in turn has a dual role in cell cycle. Hence, p53R2 can play a dual role in cell cycle progression. In addition, because p53 is the main regulator of p53R2, the mutant p53 may induce the expression of p53R2 in some cancer cells based on the "keep of function" phenomenon. Therefore, depending on the locations of p21 and the new abilities of mutant p53, p53R2 has dual role in cell cycle progression. Since the DNA damaging therapies induce p53R2 expression through the induction of p53, p53R2 can be the main therapy resistance mediator in cancers with cytoplasmic p21.

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Introduction

p53r2 and ribonucleotide reductase

Human ribonucleotide reductase, a rate-limiting enzyme complex in synthesis of dNTP, is a tetramer composed of two dissimilar homodimers including hRRM1 (R1) and hRRM2 (R2) (Fontecave et al., 1998). R1 and R2 are expressed exclusively during the S-phase. Because of the long half-life of R1, its level is constant throughout cell cycle and always in excess of the R2 level (Wang et al., 2009; Zhang et al., 2011). In the G1-phase, R2 is degraded by cadherin 1/anaphase promoting complex (Cdh1/APC) that binds to KEN box of R2 (Pontarin et al., 2007). p53R2 is a homologue of R2, and its gene contains a p53-binding site in intron 1 and encodes a 351-amino acid peptide that shows remarkable resemblance to R2 subunit of RR (Nakamura, 2004). Since p53R2 does not have a KEN box, it is not degraded in G1-phase. Therefore, during G1, p53R2 associates with R1 instead of R2 and subsequently provides dNTP for DNA repair in G1 (Chang et al., 2008; Pontarin et al., 2007; Zhang et al., 2011). While p53R2 expression is regulated in a p53-dependent manner in result of DNA damage in G1-phase(Tanaka et al., 2000), RRM2 expression is dictated by cell cycle-associated factors, such as nuclear factor Y and E2f during S-phase(Chabes et al., 2004). Thus, there are two independent pathways that supply deoxyribonucleotides: (i) through R2 in S-phase and (ii) through p53R2 for DNA repair in cells arrested in G- or G2-phase(Yamaguchi et al., 2001).

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The maximal level of p53R2 has been detected at G1/S transition (Wang et al., 2009). Furthermore, p53R2 up-regulates P21 and down-regulates cyclin D (Zhang et al., 2011), causing cell cycle arrest in G1 and providing both time and dNTP for the repair of damaged DNA. But despite these facts, the deregulated expression of p53R2 has been found in various human cancer cells. The relationship between p53R2 expression and a number of cancer cells has been listed in Table 1.

Mutant p53, gain, and "keep of function" phenomenon

Since mutant p53 (*mt*-p53) has been found in approximately 50% of human cancers, p53 was named as guardian of genome (Levine, 2011). Wild-type (wt) p53 acts as a homotetramer transcription factor that activates transcription of several hundred genes and regulates many vital biological processes, including cell differentiation, proliferation, and apoptosis (Wei et al., 2011). While mutations in most other tumor suppressor genes result in loss or aberrant synthesis of the gene product, most p53 mutations occur in DNA binding domain (residues 100–300) (Soussi and Lozano, 2005), and therefore mutant p53 can gain new functions in cell migration, invasion or metastasis (Muller et al., 2011). The accumulation of mutant p53 in nucleus can exert a dominant negative role by oligomerization with wt p53 expressed by the wt-allele (Michalovitz, 1991). Three scenarios have been proposed to explain the effects of mutant p53 in tumor biology, which are not mutually exclusive: (i) mutations in p53 result in loss of tumor-suppressive functions of wt p53 solely; (ii) mutations of p53 may lead to loss of certain tumor-suppressive functions of wt p53, while retaining and/or exaggerating other normal wt p53 function; and (iii) *mt*-p53 proteins can gain truly neomorphic functions that promote tumor growth. Such activities of *mt*-p53 are commonly attributed to one of two primary mechanisms: (i) an interaction between *mt*-p53 and cellular proteins, for instance through the inhibition of p63 and p73, which are responsible for the induction of apoptosis (discussed below), or (ii) *mt*-p53-mediated regulation of novel target genes, e.g., *mt*-p53 proteins can up-regulate genes that inhibit apoptosis or promote chemoresistance (Freed-Pastor and Prives, 2012) or can activate multidrug resistance genes (ABCB1, ABCC1, ABCG1, and MVP), growth factor receptor genes (EGFR, bFGF, and VEGF), and oncogenes (c-Myc, c-Fos, and Ras) (Denisov et al.).

P21

One of the best known p53 targets genes is p21, a small 165 amino acid protein (also known as WAF1, CIPl, SDIl, and MDA-6), which regulates various cell cycle progression associated genes such as cyclin E and cyclin A/CDK complexes to cause p53-dependent G1 growth arrest (Abbas and Dutta, 2009; Gartel et al., 1996). P21 mediates its functions through several mechanisms: (i) P21 binds to and inhibits CDK2 and CDK1 expression, arresting cell growth by inhibition of the phosphorylation of Rb by CDKs (Polager and Ginsberg, 2009); (2) P21 competes for binding to proliferating cell nuclear antigen (PCNA) with DNA polymerase-δ and several other proteins involved in DNA synthesis, thus directly inhibiting DNA synthesis (Cayrol et al., 1998); and (iii) p21 activates p21-activated kinases (Kumar et al., 2006). P21 disrupts the interaction between CDK and its substrates such as members of Rb family (p107, p130, and Rb) and CDC25 (a tyrosine phosphatase that dephosphorylates the cyclin B-bound CDK1 that is essential for entry into mitosis) and leads to cell cycle arrest (Harbour and Dean, 2000; Hartwell and Kastan, 1994). Contrary to growth-inhibitory functions, recent evidence shows that cytoplasmic p21 has an important role in cell cycle progression and cell survival (Perez-Tenorio et al., 2006) and protecting cell against of apoptosis (Asada et al., 1999). Cytoplasmic p21 has been detected in many human malignancies and correlates positively with aggressive tumors and poor prognosis because it may acquire an anti-apoptotic gain of function in the cytoplasm (Abbas and Dutta, 2009; Blagosklonny, 2002). The mechanism of cytoplasmic localization of p21 remains to be studied, but it has been revealed that the phosphorylation of P21 in Thr145 and Ser146 residues or truncation of nuclear localization signal (NLS) of p21 can result in cytoplasmic localization of P21 (Goh et al., 2011; Perez-Tenorio et al., 2006). The main enzyme thought to be responsible for P21 phosphorylation at these residues is Akt1, also known as PKB. The activation of PKB/Akt pathway by the erbB2 receptor is partially responsible for the phosphorylation of P21 at these residues (Abukhdeir and Park, 2008; Perez-Tenorio et al., 2006). The phosphorylation of P21 by Akt/PKB at Thr 145 in the PCNA-binding site disrupts its binding to PCNA (induces the cytoplasmic accumulation of p21), whereas the phosphorylation of Ser146 significantly increases the stability of p21 protein (Cayrol et al., 1998; Li et al., 2002). Akt can also be activated through other genetic alterations, including phosphoinositide 3-kinase activation from oncogenic mutations of PIK3CA, PTEN loss, or HER2/neu (ERBB2) amplification (Abukhdeir and Park, 2008). Cytoplasmic p21 inhibits a number of proteins involved in apoptosis such as procaspase 3 (phosphorylated p21 by PKB binds to procaspase 3 and procaspase3/p21 complex, induces resistance to Fas-mediated apoptosis), caspase 8, caspase 10, stress-activated protein kinases (SAPKs), and apoptosis signal-regulating kinase 1 (Abbas and Dutta, 2009; Schepers et al., 2003). Furthermore, P21 can up-regulate the genes encoding anti-apoptotic factors. P21 also down-regulates the pro-apoptotic genes by MYC and E2F1 through direct binding and inhibition of their transactivation functions (Abbas and Dutta, 2009).

Table 1
The effect of p53R2 expression on cancer cell progression or therapeutic resistance.

Type of cancer cell	p53R2 level	Remarks	Reference
Colon adenocarcinoma	High	p53R2 is negatively related to metastasis of colon adenocarcinoma and high level of p53R2 is correlated with markedly better survival in CRC patients	X. Liu et al. (2011), X. Liu et al. (2007)
Squamous cell carcinoma	High	High level of p53R2 is related to tumor development and resistance against chemo-radiation therapy	Okumura et al. (2006)
Gastric cancer	Basal (or decreased)	There is not an association between stage, grade, and progression of gastric cancer cell and p53R2	Byun et al. (2002)
Human oral cell carcinoma cell lines, SAS (p53 wild-type), HSC-4 (p53 mutant), Ca9-22 (p53 mutant), and human breast carcinoma cell line, MCF7 (p53 wild-type)	High	High expression of p53R2 was significantly associated with tumor size, lymph node metastasis, and histological differentiation and tumor was more resistant to 5-FU	Souichi Yanamoto et al. (2005)
Oral squamous cell carcinomas	High	p53R2 was significantly associated with tumor size, lymph node metastasis, and histological differentiation	S. Yanamoto et al. (2003)
Melanoma cancer	High	p53R2 was significantly correlated with the depth of invasion, the tumor stage, and chemoresistance	Matsushita et al. (2012)
Prostate cancer	High	p53R2 is associated with drug resistance	Devlin et al. (2008)
Non-small cell lung cancer	High	High level of p53R2 may be a marker of the malignant potential of lung cancer	Uramoto et al. (2006)