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Commentary

Polymorphism of p53 in cancer prognosis

Oncogenic activity or loss of tumour suppressor function results from genetic alterations within tumour cells, which finally leads to abnormal gene expression. *TP53* gene is a well-studied tumour suppressor gene. p53 is one of the key transcription factors which regulate many cellular events, such as cell cycle, DNA damage repair, apoptosis and stress response[1]. Half of all human malignancies, including colon, bone, lung, breast, lymphoma, cervical, skin, gastric, ovary, brain and urological cancers, exhibit *TP53* mutations, either in a single hotspot or at multiple sites, frequently accompanied by wild-type *TP53* inactivation[2].

After p53 gene discovery, several studies have been done on how the mutational status of this gene is important in different cellular functions; the codon 72 polymorphism is one of the crucial and most studied gene alternations, which has been reported to be associated with many cancers[1,2]. A single nucleotide polymorphism (SNP) in exon 4 results in expression of either arginine (72R) or proline (72P) at codon 72 of *TP53*. This polymorphism is located in a proline-rich domain, which is essential for its DNA-binding ability to induce apoptosis. The two genetic variants (Pro 72 and Arg 72) have been thought of having different functional activities. Marin *et al*[3] have reported that some tumour-derived *TP53* mutants can bind to *TP73* and inactivate its biofunction. Moreover, this binding activity of *TP53* mutants can be interrupted if the *TP53* variants are encoded by codon 72, a common polymorphism in the human population. Generally, Arg72 might retain a less prohibitory effect to avoiding mutant *TP53* binding to *TP73*. The *TP73* gene, a *TP53* homologue, can activate *TP53*-responsive promoters and induce apoptosis in cells deficient of *TP53*. The ability of mutant *TP53* to bind *TP73*, neutralize *TP73*-induced apoptosis and transform cells in cooperation with EJ-Ras was enhanced when codon 72 encoded Arg[2]. The Arg72 variant also appeared to interact more effectively with human papillomavirus (HPV)-E6 *in vitro* and degrade easily through the ubiquitin-proteasome pathway, resulting in inactivation of *TP53* gene and induction of HPV-related tumour development[2]. Thomas *et al*[4] have reported that Arg72 acts dominantly in transcriptional regulation of *TP53* downstream targets that induce apoptosis or repress the transformation of primary cells. It has been shown that other than gain of function mutations, genetic polymorphism also plays crucial role in carcinogenesis. The Pro72 variant is crucial for specifically activating the *TP53*-dependent DNA repair genes in different cells, resulting in higher DNA-repair efficiency *in vitro*. Furthermore, Pro72 variant-expressed cells exhibit reduced micronuclei formation, compared with Arg72, suggesting that genomic instability is reduced in these cells[2].

The interaction of HPV-E6 with *TP53* gene was suggested as the most important cellular event resulting in HPV-associated carcinogenesis, but a few reports have corroborated this finding; there was even a lack of information on the role of the *TP53* codon 72 polymorphism in the development of HPV-E6-associated cancers[5,6]. Although no association between the *TP53* codon 72 polymorphism and HPV-E6-related cancers was found, some reports stated that Arg72 homozygosity was associated with the carcinogenesis of breast cancer and bladder cancers[2]. *TP53* codon 72 polymorphism was also found to be associated with oesophageal, colorectal, chronic myeloid leukaemia (CML) and lung cancer.

Yang *et al*[7] investigated *TP53* codon 72 polymorphisms in 435 patients with oesophageal squamous cell carcinoma (ESCC) and 550 cancer-free individuals from the same geographical region. The *TP53*Arg/Arg genotype was significantly increased in ESCC cases compared with the controls. Regarding Pro72 homozygosity, Wang *et al*[8] investigated the *TP53* codon 72 polymorphism in 194 lung cancer patients and

152 non-cancerous controls in a Taiwanese population and it was suggested that the Pro72 variant might represent a risk allele associated with an increased risk of lung cancer among women. They further suggested that the *TP53* codon 72 polymorphism might also play a role in cancer susceptibility and prognosis in a specific subgroup of lung cancer patients in Taiwan[8]. Bergamaschi *et al*[9] found that the Pro72 allele occurred more frequently in patients with CML than in controls, and among CML patients who had no cytogenetic response rather than among responders. Zhu *et al*[10] examined the association between the *TP53* codon 72 polymorphism and colorectal cancer risk in 345 patients with colorectal cancer and 670 controls in a Chinese population. They concluded that the p53 codon 72 polymorphism may contribute to the aetiology of colorectal cancer in Chinese population, particularly among alcohol consumers.

TP53 variant 72 has been widely studied in different cancer in terms of onset of cancer as well as prognosis. Whether the variant (Arg72 or Pro72) is important or dominantly associated with cancer development or prognosis is still uncertain and paradoxical. The *TP53*-Arg72 and *TP53*-Pro72 variants play important roles in influencing the chemotherapeutic response of various cancers *in vitro* and *in vivo*[11]. However, findings regarding whether expression of either of the variants is important to cancer therapy are inconclusive. Another limitation of looking at *TP53* 72 codon polymorphism is that it could have ethnicity bias[12]. The p53 codon 72 arginine polymorphism does not appear to represent a risk factor for the development of cervical cancer in the UK population[13]. As infection with cancer-associated HPV types is relatively common among cytologically normal women, other environmental or genetic cofactors are required for cervical carcinogenesis. It may be that the virus load or the status of HPV integration influences the susceptibility to HPV-associated cancers. An association with human leucocyte antigen specificity has been found among both cervical cancer and cervical intraepithelial neoplasia patients, and a strong interaction between tobacco smoke and HPV-16 is indicated[6].

Earlier studies showed that there is no association between *TP53* codon 72 polymorphism and cervical cancer risk[13,14], and as tumour environment and intratumoral heterogeneity also play a role in disease prognosis, *TP53* codon 72 polymorphism status alone may not be sufficient enough for prognosis of cancer patients. Other important genes regulating cancer onset/progression also must be looked for mutations and polymorphism along with *TP53* polymorphism status for making a better conclusive statement regarding cancer prognosis and onset. As other factors such as smoking, geographical location and cancer-related viral infections could also have effect on gene polymorphism studies, so all these factors should be taken into consideration for better prognosis of cancer patients.

Like many other studies conducted on role of codon 72 polymorphism and cancer risk and survival, the study by Bansal *et al*[15] in this issue has not put light on other crucial biological as well as genetic factors which could affect the onset of disease along with prognosis. As this study showed a relation between p53 72 codon polymorphism and cervical cancer prognosis in the Indian patients, this has to be validated in a larger sample to confirm this association and to include it as one of the risk or prognosis factors in cervical cancer.

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