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Genomic Instability: The Pivotal Role of Mutant P53 in Human Cancers

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Abstract

The tumor suppressor p53 plays a critical role to preserve DNA fidelity from diverse insults through the regulation of cell-cycle checkpoints, DNA repair, senescence and apoptosis. The TP53 is altered in more than half of human cancers. This leads to the production of mutant p53 proteins that loose wild type p53 tumor suppression functions and concomitantly acquire new oncogenic deleterious features implicated in: increased cell proliferation, increased chemoresistance, disruption of tissue architecture, promotion of migration, invasion and metastasis and several other pro-oncogenic properties. Accumulating evidences suggest that mutant p53 proteins drastically perturb the residual genome-stabilizing mechanisms during cancer progression, thereby increasing genomic instability of mutant p53 carrying human cancers. In this commentary we briefly summarize the most important evidences suggesting that mutant p53 plays a relevant role in promoting genomic instability in human cancers.

Keywords: Mutant p53 proteins; Gain of function (GOF); Genomic instability; DNA repair; cancer

Introduction

In the recent few years, several consortia have led the sequencing of human cancer genomes identifying a myriad of genomic and chromosomal alterations in many human cancers [1-12]. Among them, the gene most commonly mutated is TP53: 96% in ovarian serous carcinoma [8], 85% in small cell lung cancer [6,9], 75% in pancreatic cancer [10], 60% in head and neck squamous cell carcinoma [11], 54% in invasive breast carcinoma [12], just to tell a few. 74% of p53 mutations are missense mutations that fall within its central DNA-binding domain conferring new oncogenic properties (GOF) that contribute to growth advantage of tumour cells [13]. Moreover, certain mutations in the TP53 have been associated with poor clinical outcome in several human tumours [14,15]. In line with this, in patients affected by the Li-Fraumeni (LF) syndrome, germline missense p53 mutations have been associated with earlier age of tumour onset when compared to germline TP53 loss [16]. Concerning the molecular mechanisms through which mutant p53 proteins exert their oncogenic functions, we and others previously characterized their ability to modulate gene expression through interaction with known transcription factors, such as NF-Y, YAP1, E2F1, NF-kB, Pin1 and VDR [17-21]. Mutp53 proteins also bind to p53 family members, p63 and p73 impairing their transcriptional activity and consequently their anti-tumoural effects [22-24]. In this scenario mutant p53 operates as a co-factor able to sustain the expression of several pro-oncogenic genes [11]. Mutations of TP53 are typically seen in the later clinical stages of tumors. In line with the oncogene-induced DNA damage model, activated oncogenes induce in both precancerous lesions and established cancers an aberrant DNA damage response (DDR), the failure of DNA replication forks regulation and the formation of DNA double strand breaks (DSBs) [7,25,26]. This continuous accumulation of DNA alterations activates TP53, which exerts its safeguard mechanism by promoting apoptosis or senescence [5,25-27]. When this replicative stress causes the mutation of TP53, the DDR is definitively compromised allowing cancers to develop and to spread [7,25-27].

Genomic instability is defined as an increase in the rate of DNA alterations compared to normal cells. There are diverse types of genomic instability and GOF p53 mutants have been implicated in promoting two types of instabilities, chromosomal (CIN) and amplification (AIN) instability [25-28]. Notably, expression of mutp53R172H (corresponding to human R175H) in p53-null primary mouse mammary epithelial cells and developing mouse mammary tumours resulted in aberrant centrosome amplification, multipolar mitoses and increased numbers of chromosomes [28,29].

Recently, we have shown that transcriptional activity of GOF mutant p53 proteins plays a role in the inefficient activation of DNA repair mechanism and consequent DNA damage accumulation in proliferating tumour cells [30]. In search for co-factors sharing mutant p53-induced transcriptomic alterations in cancer cells, we identified the transcriptional inhibitor E2F4 as a new partner of mutant p53 proteins in diverse types of tumoural cells. E2F4 plays an important role in the suppression of proliferation-associated genes and recent evidences report that E2F4 may play an oncogenic rather than a tumor suppressor role in cancer cells [31]. We found that mutant p53/E2F4 oncogenic complex was recruited onto rad17 and brca1 gene promoters inhibiting their expression. *Both BRCA1 and RAD17* proteins are key signal transducers during checkpoint activation in the response to DNA DSBs [32].

Our observations about epigenetic changes in the rad17 and brca1 promoters due to the concomitant recruitment of mutant p53 and E2F4 proteins provide evidenced a global increase of histone H3 methylation and a decrease of histone H4 acetylation [30]. This might contribute to chromatin transcriptional inactive status of rad17 and brca1 promoter regions. These findings might have clinical relevance. Interestingly we have assessed rad17 and brca1 gene expression in a cohort of tumors from head and neck squamous cell carcinoma (HNSCC) patients where TP53 status was assessed by direct sequencing of exons 2 through 11 [33]. HNSCC is characterized by a

high grade of genomic instability and a TP53 mutation incidence of nearly 62% [34]. We observed that rad17 and brca1 were expressed at lower level in tumors when compared to non-tumoral matched samples. This was significantly striking in the group of patients carrying mutant p53 proteins independently from other clinic-pathological parameters. Unlike those with mutant p53, wild type p53 tumors did not show any significant difference for rad17 expression between tumor and normal groups. Interestingly, brca1 transcript was upregulated in wild type p53 tumors [30]. We also found that tumors carrying missense mutations of TP53 (usually related to gain of function activities) exhibited lower expression levels of brca1 and less pronounced for rad17 when compared with a selected group of tumors, characterized by nonsense (NS) mutations and frameshift (FS) mutations. [30]. Collectively, these findings strongly support the hypothesis of an active repression of rad17 and brca1 gene expression by mutant p53 proteins, leading to a continuous DNA DSBs accumulation with a permanent increase in genomic instability.

Conclusion

The oncogene-induced DNA damage model for tumor progression can explain many characteristics of a given tumor as its high proliferation rate, its genomic instability and the uncoupling between the constitutive DDR signaling and DNA repair activity.

In the context of this intricate puzzle we propose that mutant p53 protein, on the one hand, constitutevely suppresses DNA repair activity inhibiting at least the transcription of brca1 and rad17 genes [30] and, on the other hand, it sustains aberrant cell proliferation inducing the transcription of cell cycle-related genes [17].

Of course, there are still many unresolved questions surrounding the role of mutant p53 in cancer. The answers to these questions might facilitate the development of mutant p53-tailored anticancer drugs and therapeutic strategies. This will surely benefit from studies on mutant p53 gain of function activities which mainly aim to better define the molecular events and consequently to tailor more accurately target specificity for novel therapeutic approaches.

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