TP53 Mutations and Lung Cancer: Not All Mutations Are Created Equal

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Mutations in TP53 are common in non–small cell lung cancer. Apart from the loss of tumor-suppressor functions, TP53 mutations may result in gain of function favoring cellular proliferation, inhibition of apoptosis, and genomic instability. Some TP53 mutations are more likely to affect the course of the disease than others. Clin Cancer Res; 20(17); 4419–21. ©2014 AACR.

In this issue of Clinical Cancer Research, Molina-Vila and colleagues address the prognostic significance of TP53 mutations in patients with advanced non–small cell lung cancer (NSCLC), keeping the functional impact of specific TP53 mutations in mind (1). The complex genomic landscape of lung cancer induced by tobacco smoke is characterized by numerous single-nucleotide variations, gene amplifications, deletions, and structural variants as outlined recently by The Cancer Genome Atlas Project (TCGA; ref. 2). Among several novel variants reported, one gene stands out in lung cancer and other cancers—TP53 (3). Since the initial discovery of this “master regulator” and “guardian of the genome,” more than 50,000 articles have been published on TP53 to date; much has been learned, yet there is more to be understood. That wild-type TP53 is a bona fide tumor suppressor and mutant TP53 acquires novel functions facilitating survival of cancer cells against all odds is not in doubt. However, the clinical implications of TP53 mutations in lung cancer are not so clear. Does the presence of TP53 mutations portend a poor prognosis? Do all mutations in TP53 produce the same effect functionally and clinically? Can targeting mutated TP53 become the Holy Grail of cancer therapy?

p53 (encoded by the gene TP53) is a stress response protein that mediates the transcription of genes in response to genotoxic stress, oncogenic signaling, DNA damage, and cellular injury. Like most transcription factors, p53 has a transactivation domain (TA), DNA binding domain (DBD), and tetramerization and regulatory domain (TD). Expression of p53 protein is largely controlled through its degradation by the mouse double minute 2 (MDM2) E3 ligase and a related protein, MDM4. In addition, posttranslational modification of p53 by various kinases/phosphatases and acetylases/deacetylases regulates its activity. The majority of the mutations in TP53 are either missense or nonsense mutations. Mutations in TP53 can result in one of three possible outcomes—mutations that interfere with its tumor-suppressor properties (loss of function), mutations that confer the protein with a dominant-negative phenotype, where it binds and inactivates coexpressed functional wild-type TP53, and conformational mutations that contribute to the emergence of new functions [gain of function (GOF)]. GOF mutations contribute to genomic instability, inhibition of apoptosis, cell migration, and drug resistance. GOF mutations usually engage in molecular interactions that either result in the binding and inactivation of TP53-related proteins such as TP63 and TP73, or interactions with other transcriptional factors, resulting in the novel regulation of expression of several genes (3).

Almost all small-cell lung cancers and more than half of NSCLCs harbor alterations in TP53. Although TP53 mutations are predominantly G-to-T transversions and deletions in tobacco smokers, such alterations are infrequent in never-smokers. Studies that investigated the role of TP53 mutations as a prognostic marker in NSCLC have reported conflicting results (4–10). These conflicting findings may be due to the molecular heterogeneity and differing functional effects specific to various TP53 genotypes, methodologic issues related to the assessment of mutation status, and design issues related to small sample size and nonhomogeneous groups of patients. Finally, the context in which these mutations occur, the initiating events and other secondary molecular alterations, may matter as well.

Instead of treating all TP53 mutations in the same way to assess their clinical impact, it may be sensible to categorize them in different groups based on the functional effects they induce, i.e., loss of tumor-suppressor effect versus GOF. Mutations involving TP53 can be classified from a structural viewpoint as “contact mutations” that affect residues directly involved in sequence-specific DNA contacts but do not alter the conformation of the p53 molecule (prototype hotspot mutation, R273H) and "conformational mutations" resulting in partial or complete loss of normal conformation of wild-type p53 (prototype hotspot mutation,
R175H; ref. 11). Conformational changes can interfere with the recognition of DNA binding elements that are normally recognized by wild-type TP53 and uncover hitherto hidden interfaces in these DNA binding domains. Another practical way to categorize TP53 mutations is as disruptive or non-disruptive based on the location of the mutation and the predicted amino acid alterations (12). Mutations resulting in the substitution of amino acids belonging to a different polarity and charge in the L2 and L3 regions of the DNA binding domains, or stop codon, are classified as disruptive. All other mutations are categorized as nondisruptive. Importantly, these mutations have already been characterized for their cellular effects using human cell systems and mouse models. Many nondisruptive variants are GOF mutations that mediate oncogenesis through mechanisms already described.

Molina-Vila and colleagues examined retrospectively the impact of TP53 mutations in 318 patients with stage IIIB–IV NSCLC, including 125 patients with EGFR mutations (1). In the group of patients with EGFR wild-type
NSCLC, the median overall survival was significantly lower in those with nondisruptive TP53 mutation than those whose tumor cells had either wild-type TP53 or with a disruptive TP53 mutation (8.5 months vs. 15.6 months respectively, \( P = 0.003 \)). This difference was seen even in the EGFR-mutant group (17.8 months vs. 28.4 months, \( P = 0.04 \)), underscoring the significant effect of nondisruptive TP53 mutations independent of EGFR status. These findings were confirmed in a small independent cohort of patients with EGFR-mutant NSCLC. However, these findings are directly in conflict with the results from Poeta and colleagues (12), who reported worse outcomes in early-stage head and neck cancers harboring disruptive TP53 mutants. It is possible that specific TP53 mutants may exert unique and seemingly conflicting effects based on the tissue of origin and concomitant genomic alterations. Clearly, more studies need to be done to validate or refute these observations.

Fortunately, ongoing studies by TCGA and other large-scale genomic studies will provide a large body of information on TP53 mutation status from several thousand patients with NSCLC (Fig. 1). Integration of transcriptomic and proteomic studies will enable us to tease out the downstream effects of the various classes of TP53 mutations in the coming years. Parsing these data carefully using well-curated clinical specimens and follow-up functional studies will shed more light on the in vivo effects of various mutations involving TP53.

Disappointingly, therapeutic strategies directed toward TP53 alterations have largely failed. Many such strategies focused on the reactivation of TP53 in cancer cells, with the hope of restoring its tumor-suppressor properties. Characterizing the downstream pathways activated by TP53 GOF variants is a critical first step before developing therapies aimed at functionally reestablishing the master regulator that goes awry in so many cancers.

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No potential conflicts of interest were disclosed.

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