NEK2, a promising target in TP53 mutant cancer

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In human cancers, aberration of tumor suppressors and oncogenes cooperate to contribute to tumor initiation and progression.[1,2]TP53, one of the best-known tumor suppressors, appears to have diverse roles through working together with different oncogenes.[3,4] A good example is *RAS* mutations co-occurring with *TP53* lesions. *KRAS* hyper-activation leads to cell replicative senescence, which could be overcome by lesions in *TP53*, escaping immune clearance surveillance and promoting tumorigenesis. In the current issue of *Adv Sci* 2022, Feng et al expand the significance of *TP53* loss to drug resistance through co-regulating oncogene *NEK2* amplification/gene overexpression with multiple myeloma (MM) as a disease model.[5]

In this paper, the authors set out the study with systematic identification of the correlation between *TP53* genetic lesion and amplification/overexpression of *NEK2* in MM through data mining of public available datasets. This led to the discovery of

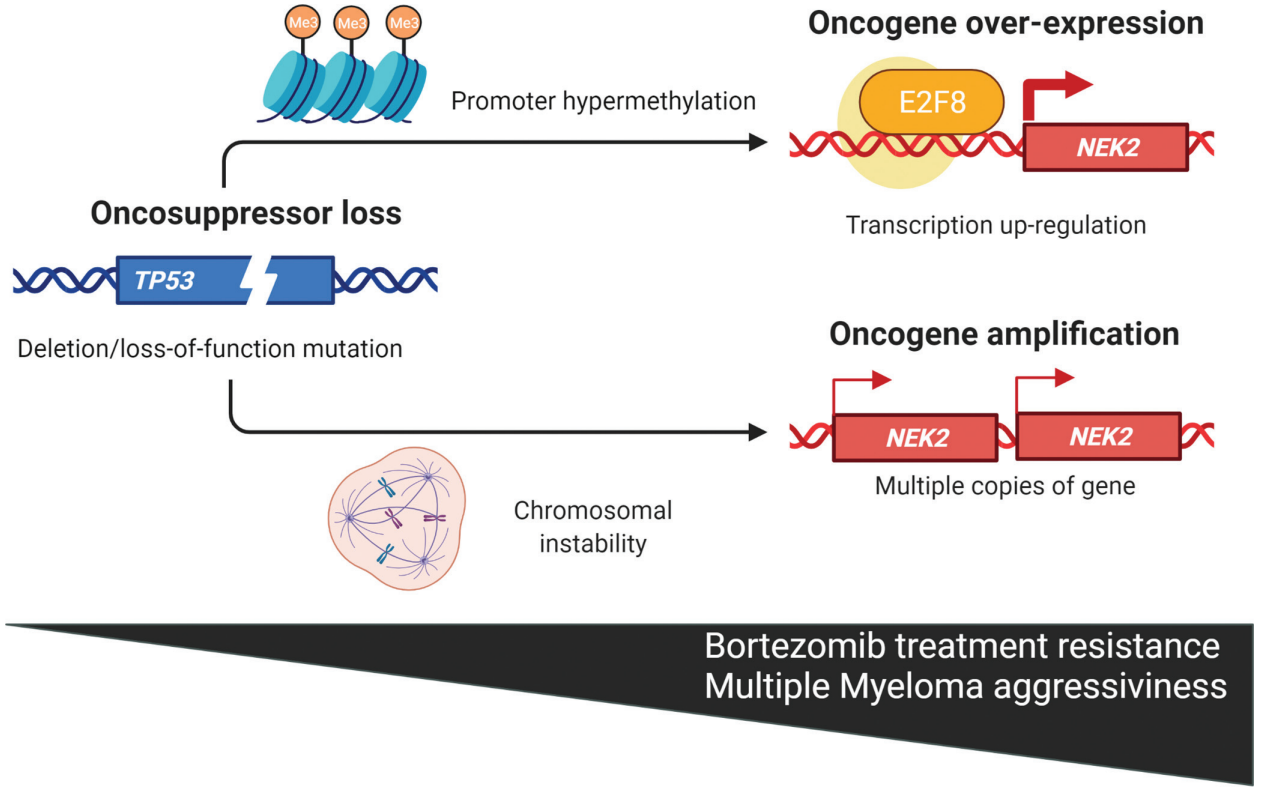

Figure 1. *TP53* genetic lesions promote *NEK2* abundance by regulating gene expression and oncogene amplification. *TP53* genetic lesions employ multiple molecular mechanisms to regulate *NEK2* abundance, which either by increasing promoter hypermethylation to control gene expression or by inducing chromosomal instability to modulate copy number of *NEK2*. Combined defects in *TP53* and *NEK2* render multiple myeloma cells drug resistance to Bortezomib.

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co-occurrence between *TP53* deletion and *NEK2* amplification/overexpression, which is significantly associated with poor overall survival in MM. Of note, this synergy is a shared feature across various cancer types as TCGA data reanalysis confirmed this observation, indicating a high priority to understand the molecular mechanism for this co-occurrence as well as its clinical implication (Fig. 1).

The authors first established a causal relationship between *TP53* deletion and *NEK2* gene overexpression/amplification using MM cell lines with and without *TP53* allele. Loss of *TP53* gene led to differential expression of genes involved in cell cycle, methylation control, and chromosomal stability, resulting in the transcriptional hyper-activation of *NEK2* through down-regulating methyltransferase (eg, *DNMT)* and up-regulating *E2F* genes. Moreover, *TP53* loss also promoted the acquisition of multiple copies of *NEK2* by increasing genomic instability. Consequently, *NEK2* activation and *TP53* suppression caused mitotic aberrations, tumor proliferation, and disease progression in MM. All these phenotypes can be reversed by overexpression of wildtype *p53*, highly suggesting that *TP53* loss unleash *NEK2* amplification/overexpression to boost cancer cell genomic instability and proliferation. *NEK2* was previously reported to induce drug resistance through activation of efflux drug pumps.[6] The authors then tested if *TP53* loss/NEK2 over-expression may form the basis of drug resistance to contribute to the disease aggressiveness. Using MM front line therapy Bortezomib (BTZ) as an example, they demonstrated that silencing of *NEK2* in *TP53* depleted MM cells sensitized these cells to the drug treatment and impaired cell proliferation. Stable expression of wildtype p53 enhanced the therapeutic effect of BTZ both in vitro and in vivo with further improvement upon *NEK2* depletion. Altogether, these results suggest that targeting the function of the NEK2 and p53 pathways may have therapeutic values by reversing the adverse outcome of MM patients without p53.

As one of the most frequently mutated/deleted tumor suppressors in cancer, *TP53* genetic lesions are often associated with poor overall survival; hence, it is a good therapeutic target. However, most of the lesions produce generally inactive proteins, making it challenging with drugs. The current strategy has been focusing on restoring wildtype p53 function with small molecules or other means.[7-10] This discovery illustrates that targeting *NEK2* kinase in *TP53* mutated/depleted cancers could be an alternative strategy. In this light, the development on NEK2 kinase inhibitors and testing their efficacy alone and in combination with gold standard treatment would be a priority in MM and maybe other tumor types. In this scenario, investigation of synergy between lesions in *TP53* and *NEK2* in other tumoral contexts would be beneficial. Although a causative link was established in this current study, some MM samples with *TP53* deletion but without *NEK2* overexpression/amplification remains to be further investigated for their antagonist mechanism (s) in controlling this synergy.

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