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Novel mechanism links p63 and cisplatin resistance

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Cisplatin, a small-molecule platinum compound, is one of the most effective broad-spectrum anticancer drugs. In the clinic, patients usually have a good initial response to cisplatin-based chemotherapy but later relapse because of the development of cisplatin resistance. This resistance is either acquired or intrinsic and markedly reduces the drug's clinical effectiveness. At the moment, this complex, resistant mechanism remains an overarching challenge due to the pleiotropic phenotype associated with cisplatin resistance.

p63, a p53 homolog gene, has 6 different isforms (TAp63α, β, γ and ΔNp63α, β, γ) due to 2 promoters and differential splicing of the p63 COOH terminus. ΔNp63 and TAp63 demonstrate opposing regulatory functions on downstream target genes.[1,2] Accumulating evidence supports the notion that TA isoforms of p63 act similarly as wild-type p53, while ΔN isoforms of p63 are more like mutant p53.[3,4] ΔNp63α attracted the most attention, because it is the most abundantly overexpressed isoform of p63 in various human cancers, including squamous cell carcinoma (SCC). However, its functional role as an oncogene in tumorigeneisis or chemoresistance remains elusive.

Recently, Ratoviski's group discovered that the SCC cells exposed to cisplatin treatment displayed a dramatic downregulation of ΔNp63α via an ATM-dependent phosphorylation mechanism, suggesting the critical role of ΔNp63α in modulating sensitivity of SCC to cisplatin treatment.[5] Further study from this group showed that the phosphorylated (p)-ΔNp63α protein is critical for the transcriptional regulation of downstream mRNAs and microRNAs in SCC cells upon cisplatin exposure.[6] Moreover, the specific microRNAs downregulated or upregulated in SCC cells in response to cisplatin treatment are involved in a broad plethora of cellular processes, including apoptosis autophagy and various metabolic and signaling pathways.[7]

In a paper published in the March 1, 2014 issue of *Cell Cycle*, Ratoviski continued efforts in deciphering the role of the cisplatin-induced TP63-regulated microRNAs, specifically in epigenetic regulation and chemoresistance.[8] By comparing SCC models with knock-in of wild-type and phosphorylation-deactivating mutant ΔNp63α, the author showed that cisplatin exposure of SCC-11 cells led to an upregulation of miR-297, miR-92b-3p, and miR-485–5p through a phosphorylated ΔNp63α-dependent mechanism. These microRNAs subsequently modulated the expression of the protein targets implicated in DNA methylation (DNMT3A), histone deacetylation (HDAC9), and demethylation (KDM4C). Moreover, the author showed that there is increased ΔNp63α binding to these proteins in Cisplatin-resistant cells (SCC-11M) compared with sensitive cells (SCC-11). Using the chromatin immunoprecipitation (ChIP) assay, the author demonstrated that ΔNp63α bound more efficiently to DAPK1, SMARCA2, and MDM2 gene promoters in cisplatin-resistant cells than in sensitive cells, suggesting ΔNp63α forms protein complexes with epigenetic enzymes to target gene promoters. Further studies showed that mimics for miR-297, miR-92b-3p, or miR-485–5p, along with siRNA against and inhibitors of DNMT3A, HDAC9, and KDM4C, modulated the expression of *DAPK1, SMARCA2,* and *MDM2* genes assessed by the quantitative PCR and promoter luciferase reporter assays. More importantly, the above-mentioned treatments affecting epigenetic enzymes also modulated the response of SCC cells to chemotherapeutic drugs, rendering the resistant SCC cells more sensitive to cisplatin exposure. Taken together, the study above identified a novel p-ΔNp63α/microRNA network in controlling the downstream epigenetic regulatory layers. This discovery not only expands our understanding of gene transcriptional regulation, but also establishes a new scenario for the cisplatin-resistant molecular mechanism.

Probably the most significant aspect of this study is its potential clinical application. Given the technical challenge of targeting the transcriptional factors and structural similarities of ΔNp63α with other isoforms of p63 gene, specific, small molecules targeting ΔNp63α remain unavailable. The critical and essential role of the specific microRNA as another layer of regulator controlled by p-ΔNp63α could serve as novel therapeutic targets to modulate cancer cells' response to cisplatin. Future direction for this study will be to further clarify the most potent and specific microRNAs in response to cisplatin in SCC and to test their individual or combinational effects as therapeutic targets in SCC treatment. The results of these studies are expected to provide the groundwork for novel chemotherapeutic avenues in treating patients with SCC.

References

1. Osada M, et al. Mol Cell Biol 2005; 25:6077-89; PMID:15988020; http://dx.doi.org/10.1128/MCB.25.14.6077-6089.2005
2. Wu G, et al. Cancer Res 2003; 63:2351-7; PMID:12750249
3. Murray-Zmijewski F, et al. Cell Death Differ 2006; 13:962-72; PMID:16601753; http://dx.doi.org/10.1038/sj.cdd.4401914
4. Wu G, et al. Cancer Res 2005; 65:758-66; PMID:15705872
5. Huang Y, et al. Cell Cycle 2008; 7:2846-55; PMID:18769144; http://dx.doi.org/10.4161/cc.7.18.6627
6. Huang Y, et al. Cell Death Differ 2011; 18:1220-30; PMID:21274007; http://dx.doi.org/10.1038/cdd.2010.188
7. Huang Y, et al. Cell Cycle 2012; 11:1247-59; PMID:22356768; http://dx.doi.org/10.4161/cc.11.6.19670
8. Ratovitski EA. Cell Cycle 2014; 13:749 - 761; http://dx.doi.org/10.4161/cc.27676