Getting down to the FACT: therapeutic targeting of *MYC*-dependent tumors

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The *MYC* oncogene is thought to be involved in more than half of all human tumors and hence has great potential as a targeted therapy. However, despite the well appreciated role of oncogenes in the pathogenesis and maintenance of tumors, the ability to directly target them has proven elusive save a few examples, such as imatinib for chronic myelogenous leukemia. Recently, Carter *et al.* reported a way to circumvent the necessity to directly target *MYC* in neuroblastoma, a *MYC*-driven pediatric cancer, by identifying a downstream factor that was essential for the high expression of *MYC*-targeted genes in these tumors (1).

The authors began their search for targets downstream of *MYC*-driven transcription by filtering the gene-expression profiles of close to 650 neuroblastoma tumors through a *MYC* activation signature. This was followed by the application of multiple additional filters related to the level of prognostic significance as well as the current availability of a small molecule inhibitor to narrow the field down to one gene, suppressor of Ty 16 (*SUPT16H*). This gene encodes for SPT16, which along with SSRP1, forms the facilitated chromatin transcription (FACT) complex. FACT serves to remodel histones at sites of active transcription to enable processivity of the RNA polymerase (2). Using neuroblastoma cell lines, the authors revealed a previously unappreciated interdependence between *MYC* and FACT whereby *MYC* directly drives transcription of *SUPT16H* and *SSRP1* and FACT then feeds back to positively drive both *MYC* expression and protein stability. In support of this model, the cell lines with the highest levels of *MYC* expression were also the most sensitive to perturbation of FACT.

As mentioned previously, a main criteria that led the authors to focus on FACT was the current availability of an inhibitor. Specifically, an indirect inhibitor to FACT, CBL0137, has been developed and is currently in clinical trials for cancer (NCT01905228) (3). CBL0137 binds to DNA but, unlike conventional DNA intercalating agents, it is non-mutagenic and hence was shown not to induce a DNA damage response (3). Instead, CBL0137 binding to DNA causes a prevalence of alternative DNA structures and destabilized nucleosomes which FACT recognizes and consequentially becomes trapped at (4). This leads to cell death via FACT-dependent activation of p53 as well as downregulation of a subset of NF-κB-dependent genes (3). Using animal models, the authors demonstrate that neuroblastoma tumors treated with CBL0137 undergo increased apoptosis as a result of inhibition of the FACT/*MYC* positive feedback loop. This translated into a significant increase in survival for mice treated with CBL0137. Furthermore, combining CBL0137 with DNA damaging chemotherapeutics routinely used for neuroblastoma showed even greater *in vivo* efficacy versus any drug used as a monotherapy.

The synergy with DNA damaging agents is particularly interesting as it likely highlights a therapeutic efficacy of

FACT perturbation independent from deregulation of MYC. FACT has been directly implicated in aspects of the DNA damage response so it is plausible that chromatin trapping by CBL0137 would preclude the ability of FACT to contribute to this process (5-9). Alternatively, the DNA intercalation of CBL0137 in combination with another DNA-damaging agent may synergize to grossly alter DNA integrity and trigger cell death. It is somewhat surprising that CBL0137 is not genotoxic as a single agent despite its mechanism of action of directly binding DNA. Its ability to increase DNA double strand breaks was ruled out by the authors and others, by using markers for this event as well as by evaluating direct DNA laddering which is indicative of DNA breaks (3). The recent evidence that CBL0137 drives the formation of alternative DNA structures which FACT can bind and directly trigger a p53-dependent response, hence circumventing the need to activate the DNA damage response, sheds some light as to why there are not direct DNA breaks with CBL0137 treatment alone. However, this model may need to be modified in the context of combination treatment whereby Carter *et al.* demonstrated that efficacy was independent of p53 status.

Another area that would be of interest to explore further is the impact of CBL0137 on putative cancer stem-like cells in neuroblastoma. These cells represent a subpopulation in these tumors that harbor stem cell-like characteristics with a high tumorigenic potential. They were identified in both neuroblastoma cell lines and from primary tumors with more recent studies elucidating gene expression signatures unique to these cells (10-13). In previous studies, CBL0137, as a monotherapy, had a preferential impact on the cancer stem cell component in pancreatic cancer and glioblastoma and the same may hold true for neuroblastoma (14,15). FACT itself is more highly expressed in developmental tissues and likely is crucial for the regulation of stem-specific gene signatures that cancer stem-like cells are dependent on and hence more susceptible to cell death upon FACT disruption by CBL0137. It is thought that neuroblastomas are embryonal tumors that arise from a differentiation defect of multipotent embryonic neural crest cells. In support of the previously stated critical role for FACT in the undifferentiated state, Carter *et al.* confirmed that FACT was highly expressed in neuroblastoma precursor cells in a mouse model and showed that CBL0137 treatment could promote differentiation.

These studies provide new options for clinical paradigms that can be used to target *MYC*-driven tumors. They also independently shine a light on FACT disruption, via CBL0137, as a promising therapeutic modality. The author's data hold promise for the clinical application of this approach for neuroblastoma, which remains difficult to treat in advanced stages. More broadly, with *MYC* alterations so common in numerous tumor types, these findings provide rational to test this treatment strategy for other cancers.

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Footnote

Conflicts of Interest: The author has no conflict of interest to declare.

References

1. Carter DR, Murray J, Cheung BB, et al. Therapeutic targeting of the MYC signal by inhibition of histone chaperone FACT in neuroblastoma. Sci Transl Med 2015;7:312ra176.
2. Orphanides G, LeRoy G, Chang CH, et al. FACT, a factor that facilitates transcript elongation through nucleosomes. Cell 1998;92:105-16.
3. Gasparian AV, Burkhart CA, Purmal AA, et al. Curaxins: anticancer compounds that simultaneously suppress NF-kappaB and activate p53 by targeting FACT. Sci Transl Med 2011;3:95ra74.
4. Safina A, Cheney P, Pal M, et al. FACT is a sensor of DNA torsional stress in eukaryotic cells. Nucleic Acids Res 2017. [Epub ahead of print].
5. Heo K, Kim H, Choi SH, et al. FACT-mediated exchange of histone variant H2AX regulated by phosphorylation of H2AX and ADP-ribosylation of Spt16. Mol Cell 2008;30:86-97.
6. Sand-Dejmek J, Adelmant G, Sobhian B, et al. Concordant and opposite roles of DNA-PK and the "facilitator of chromatin transcription" (FACT) in DNA repair, apoptosis and necrosis after cisplatin. Mol Cancer 2011;10:74.
7. Dinant C, Ampatziadis-Michailidis G, Lans H, et al. Enhanced chromatin dynamics by FACT promotes transcriptional restart after UV-induced DNA damage. Mol Cell 2013;51:469-79.
8. Oliveira DV, Kato A, Nakamura K, et al. Histone chaperone FACT regulates homologous recombination by chromatin remodeling through interaction with RNF20. J Cell Sci 2014;127:763-72.

9. Kari V, Shchebet A, Neumann H, et al. The H2B ubiquitin ligase RNF40 cooperates with SUPT16H to induce dynamic changes in chromatin structure during DNA double-strand break repair. Cell Cycle 2011;10:3495-504.
10. Walton JD, Kattan DR, Thomas SK, et al. Characteristics of stem cells from human neuroblastoma cell lines and in tumors. Neoplasia 2004;6:838-45.
11. Ross RA, Spengler BA, Domenech C, et al. Human neuroblastoma I-type cells are malignant neural crest stem cells. Cell Growth Differ 1995;6:449-56.
12. Hansford LM, McKee AE, Zhang L, et al. Neuroblastoma cells isolated from bone marrow metastases contain a naturally enriched tumor-initiating cell. Cancer Res 2007;67:11234-43.
13. Ross RA, Walton JD, Han D, et al. A distinct gene expression signature characterizes human neuroblastoma cancer stem cells. Stem Cell Res 2015;15:419-26.
14. Burkhart C, Fleyshman D, Kohrn R, et al. Curaxin CBL0137 eradicates drug resistant cancer stem cells and potentiates efficacy of gemcitabine in preclinical models of pancreatic cancer. Oncotarget 2014;5:11038-53.
15. Dermawan JK, Hitomi M, Silver DJ, et al. Pharmacological Targeting of the Histone Chaperone Complex FACT Preferentially Eliminates Glioblastoma Stem Cells and Prolongs Survival in Preclinical Models. Cancer Res 2016;76:2432-42.

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