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Targeting condensin, a vital spot of *MYCN*-amplified neuroblastoma

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Neuroblastoma is a disease in which malignant cells form in nerve tissue. Amplification of *MYCN*, a member of the *MYC* proto-oncogene family, is frequently observed in neuroblastoma, and it is associated with malignant phenotype and poor prognosis.[1] In the April 1, 2014 issue of *Cell Cycle*, Murakami-Tonami et al.[2] reported that downregulation of SMC2, a subunit of condensin, leads to cell death through dysfunction of DNA repair specifically in *MYCN*-amplified neuroblastoma cells, suggesting that SMC2 can be an effective anti-cancer target in this type of tumor.

There are 2 types of condensin in human cells, namely condensin I and condensin II.[3] SMC2 and SMC4 are common subunits of both types of condensin. In addition, condensin I contains CAP-D2, CAP-H, and CAP-G, and condensin II contains CAP-D3, CAP-H2, and CAP-G2. From the analysis of the expression profile in *MYCN*-amplified neuroblastoma cells and transgenic mouse model, the authors found the correlation between amplification of *MYCN* and elevated expression of *SMC2*. The observed correlation was supported by the finding that N-MYC binds to E-box, a consensus MYC-binding sequence for transcriptional activation located within the intron of *SMC2*. Interestingly, amplification of *MYCN* and depletion of SMC2 leads to a synergistic lethal effect characterized by induction of apoptosis through accumulation of DNA damage. Because amplification of MYC induces DNA damage by producing relative oxygen species (ROS) or replicative stress,[4,5] the authors explored the functional link between condensin and DNA damage response (DDR). Intriguingly, they found that depletion of SMC2 leads to downregulation of DDR genes, including *BRCA1, MRE11, NBS1, RAD50*, and, *ATM*.[6] These data explain why depletion of SMC2 leads to higher sensitivity to DNA damage, especially in *MYCN*-amplified neuroblastoma cells. They also show that SMC2 interacts with MYCN, and they bind to E-box within at least *NBS1* intron, suggesting the possibility that SMC2 cooperates with MYCN for activating DDR genes. Upregulation of SMC4 and CAP-D2 (condensin I subunit), but not condensin II subunit, are correlated with poor prognosis in neuroblastoma with high expression of *MYCN*, suggesting that condensin I complex cooperates with MYCN.

Accordingly, this study suggests that targeting condensin in *MYCN*-driven neuroblastoma might promote tumor-specific retardation in cell growth and, therefore, have a therapeutic impact. If amplification of other *MYC* family genes, such as *c-MYC* and *MYCL*, causes synergetic defects with SMC2-depletion, such "condensin-targeting" strategy might be applicable to other types of tumors.

References

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