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日本語要約

Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B


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Abstract

Acquired resistance to anticancer treatments is a substantial barrier to reducing the morbidity and mortality that is attributable to malignant tumors. Components of tissue microenvironments are recognized to profoundly influence cellular phenotypes, including susceptibilities to toxic insults. Using a genome-wide analysis of transcriptional responses to genotoxic stress induced by cancer therapeutics, we identified a spectrum of secreted proteins derived from the tumor microenvironment that includes the Wnt family member wingless-type MMTV integration site family member 16B (WNT16B). We determined that *WNT16B* expression is regulated by nuclear factor of κ light polypeptide gene enhancer in B cells 1 (NF- κ B) after DNA damage and subsequently signals in a paracrine manner to activate the canonical Wnt program in tumor cells. The expression of WNT16B in the prostate tumor microenvironment attenuated the effects of cytotoxic chemotherapy *in vivo*, promoting tumor cell survival and disease progression. These results delineate a mechanism by which genotoxic therapies given in a cyclical manner can enhance subsequent treatment resistance through cell nonautonomous effects that are contributed by the tumor microenvironment.

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Contributions

Y.S. designed and conducted experiments, and wrote the manuscript. J.C. provided reagents and technical advice. C.H., T.M.B. and P.P. provided clinical materials for the assessments of treatment responses. I.C. analyzed data. L.T. analyzed tissue histology and immunohistochemical assays. P.S.N. designed experiments, analyzed data and wrote the manuscript.

Competing financial interests

The authors declare no competing financial interests.

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Supplementary information

PDF files

1. Supplementary Text and Figures (11M)
Supplementary Figures 1–7 and Supplementary Methods

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