NATURE MEDICINE **| ARTICLE**

日本語要約

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

Yu Sun, Judith Campisi, Celestia Higano, Tomasz M Beer, Peggy Porter, Ilsa Coleman, Lawrence True & Peter S Nelson

Nature Medicine **18**, 1359–1368 (2012) doi:10.1038/nm.2890

Received 25 April 2011 Accepted 08 June 2012 Published online 05 August 2012

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-κB) 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.

References

1. Longley, D.B. & Johnston, P.G. Molecular mechanisms of drug resistance. *J. Pathol.* **205**, 275–292 (2005).
2. Wang, T.L. *et al*. Digital karyotyping identifies thymidylate synthase amplification as a mechanism of resistance to 5-fluorouracil in metastatic colorectal cancer patients. *Proc. Natl. Acad. Sci. USA* **101**, 3089–3094 (2004).
3. Schmitt, C.A., Rosenthal, C.T. & Lowe, S.W. Genetic analysis of chemoresistance in primary murine lymphomas. *Nat. Med.* **6**, 1029–1035 (2000).
4. Helmrich, A. *et al*. Recurrent chromosomal aberrations in INK4a/ARF defective primary lymphomas predict drug responses *in vivo*. *Oncogene* **24**, 4174–4182 (2005).
5. Redmond, K.M., Wilson, T.R., Johnston, P.G. & Longley, D.B. Resistance mechanisms to cancer chemotherapy. *Front. Biosci.* **13**, 5138–5154 (2008).
6. Wilson, T.R., Longley, D.B. & Johnston, P.G. Chemoresistance in solid tumours. *Ann. Oncol.* **17** (suppl. 10), x315–x324 (2006).
7. Lee, S. & Schmitt, C.A. Chemotherapy response and resistance. *Curr. Opin. Genet. Dev.* **13**, 90–96 (2003).
8. Sakai, W. *et al*. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature* **451**, 1116–1120 (2008).
9. Kobayashi, H. *et al*. Acquired multicellular-mediated resistance to alkylating agents in cancer. *Proc. Natl. Acad. Sci. USA* **90**, 3294–3298 (1993).
10. Waldman, T. *et al*. Cell-cycle arrest versus cell death in cancer therapy. *Nat. Med.* **3**, 1034–1036 (1997).
11. Samson, D.J., Seidenfeld, J., Ziegler, K. & Aronson, N. Chemotherapy sensitivity and resistance assays: a systematic review. *J. Clin. Oncol.* **22**, 3618–3630 (2004).
12. Croix, B.S. *et al*. Reversal by hyaluronidase of adhesion-dependent multicellular drug resistance in mammary carcinoma cells. *J. Natl. Cancer Inst.* **88**, 1285–1296 (1996).
13. Kerbel, R.S. Molecular and physiologic mechanisms of drug resistance in cancer: an overview. *Cancer Metastasis Rev.* **20**, 1–2 (2001).

14. Wang, F. *et al*. Phenotypic reversion or death of cancer cells by altering signaling pathways in three-dimensional contexts. *J. Natl. Cancer Inst.* **94**, 1494–1503 (2002).

15. Kim, J.J. & Tannock, I.F. Repopulation of cancer cells during therapy: an important cause of treatment failure. *Nat. Rev. Cancer* **5**, 516–525 (2005).

16. Trédan, O., Galmarini, C.M., Patel, K. & Tannock, I.F. Drug resistance and the solid tumor microenvironment. *J. Natl. Cancer Inst.* **99**, 1441–1454 (2007).

17. Garzotto, M., Myrthue, A., Higano, C.S. & Beer, T.M. Neoadjuvant mitoxantrone and docetaxel for high-risk localized prostate cancer. *Urol. Oncol.* **24**, 254–259 (2006).

18. Beer, T.M. *et al*. Phase I study of weekly mitoxantrone and docetaxel before prostatectomy in patients with high-risk localized prostate cancer. *Clin. Cancer Res.* **10**, 1306–1311 (2004).

19. Bavik, C. *et al*. The gene expression program of prostate fibroblast senescence modulates neoplastic epithelial cell proliferation through paracrine mechanisms. *Cancer Res.* **66**, 794–802 (2006).

20. Coppé, J.P. *et al*. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol.* **6**, 2853–2868 (2008).

21. Clevers, H. Wnt/β-catenin signaling in development and disease. *Cell* **127**, 469–480 (2006).

22. Binet, R. *et al*. WNT16B is a new marker of cellular senescence that regulates p53 activity and the phosphoinositide 3-kinase/AKT pathway. *Cancer Res.* **69**, 9183–9191 (2009).

23. Acosta, J.C. *et al*. Chemokine signaling via the CXCR2 receptor reinforces senescence. *Cell* **133**, 1006–1018 (2008).

24. Huang, S.M. *et al*. Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. *Nature* **461**, 614–620 (2009).

25. Thiery, J.P., Acloque, H., Huang, R.Y. & Nieto, M.A. Epithelial-mesenchymal transitions in development and disease. *Cell* **139**, 871–890 (2009).

26. Yook, J.I. *et al*. A Wnt-Axin2–GSK3β cascade regulates Snail1 activity in breast cancer cells. *Nat. Cell Biol.* **8**, 1398–1406 (2006).

27. Vincan, E. & Barker, N. The upstream components of the Wnt signalling pathway in the dynamic EMT and MET associated with colorectal cancer progression. *Clin. Exp. Metastasis* **25**, 657–663 (2008).

28. Wu, K. & Bonavida, B. The activated NF-κB–Snail–RKIP circuitry in cancer regulates both the metastatic cascade and resistance to apoptosis by cytotoxic drugs. *Crit. Rev. Immunol.* **29**, 241–254 (2009).

29. Peinado, H., Olmeda, D. & Cano, A. Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype? *Nat. Rev. Cancer* **7**, 415–428 (2007).

30. Bernard, D. *et al*. Involvement of Rel/nuclear factor-κB transcription factors in keratinocyte

senescence. *Cancer Res.* **64**, 472–481 (2004).

31. Berchtold, C.M., Wu, Z.H., Huang, T.T. & Miyamoto, S. Calcium-dependent regulation of NEMO nuclear export in response to genotoxic stimuli. *Mol. Cell. Biol.* **27**, 497–509 (2007).

32. Kuilman, T. *et al*. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell* **133**, 1019–1031 (2008).

33. Kuilman, T. & Peeper, D.S. Senescence-messaging secretome: SMS-ing cellular stress. *Nat. Rev. Cancer* **9**, 81–94 (2009).

34. Fumagalli, M. & d'Adda di Fagagna, F. SASPense and DDRama in cancer and ageing. *Nat. Cell Biol.* **11**, 921–923 (2009).

35. Michaloglou, C. *et al*. BRAFE600-associated senescence-like cell cycle arrest of human naevi. *Nature* **436**, 720–724 (2005).

36. Xue, W. *et al*. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature* **445**, 656–660 (2007).

37. Wajapeyee, N., Serra, R.W., Zhu, X., Mahalingam, M. & Green, M.R. Oncogenic BRAF induces senescence and apoptosis through pathways mediated by the secreted protein IGFBP7. *Cell* **132**, 363–374 (2008).

38. Coppé, J.P., Kauser, K., Campisi, J. & Beausejour, C.M. Secretion of vascular endothelial growth factor by primary human fibroblasts at senescence. *J. Biol. Chem.* **281**, 29568–29574 (2006).

39. Gilbert, L.A. & Hemann, M.T. DNA damage–mediated induction of a chemoresistant niche. *Cell* **143**, 355–366 (2010).

40. Biswas, S. *et al*. Inhibition of TGF-β with neutralizing antibodies prevents radiation-induced acceleration of metastatic cancer progression. *J. Clin. Invest.* **117**, 1305–1313 (2007).

41. Davis, A.J. & Tannock, J.F. Repopulation of tumour cells between cycles of chemotherapy: a neglected factor. *Lancet Oncol.* **1**, 86–93 (2000).

42. Meads, M.B., Hazlehurst, L.A. & Dalton, W.S. The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance. *Clin. Cancer Res.* **14**, 2519–2526 (2008).

43. Shree, T. *et al*. Macrophages and cathepsin proteases blunt chemotherapeutic response in breast cancer. *Genes Dev.* **25**, 2465–2479 (2011).

44. DeNardo, D.G. *et al*. Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov.* **1**, 54–67 (2011).

45. Chien, Y. *et al*. Control of the senescence-associated secretory phenotype by NF-κB promotes senescence and enhances chemosensitivity. *Genes Dev.* **25**, 2125–2136 (2011).

46. Alderton, P.M., Gross, J. & Green, M.D. Comparative study of doxorubicin, mitoxantrone, and epirubicin in combination with ICRF-187 (ADR-529) in a chronic cardiotoxicity animal model. *Cancer Res.* **52**, 194–201 (1992).

Download references

Author information

Affiliations

Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
Yu Sun, Peggy Porter, Ilsa Coleman & Peter S Nelson

Buck Institute for Research on Aging, Novato, California, USA.
Judith Campisi

Lawrence Berkeley National Laboratory, Berkeley, California, USA.
Judith Campisi

Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
Celestia Higano & Peter S Nelson

Department of Medicine, University of Washington, Seattle, Washington, USA.
Celestia Higano & Peter S Nelson

Division of Hematology and Medical Oncology, Oregon Health and Science University, Portland, Oregon, USA.
Tomasz M Beer

Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon, USA.
Tomasz M Beer

Department of Pathology, University of Washington, Seattle, Washington, USA.
Lawrence True & Peter S Nelson

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.

Corresponding author

Correspondence to: Peter S Nelson

Supplementary information

PDF files

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

Nature Medicine ISSN 1078-8956 EISSN 1546-170X