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## Short Communication

# The Paradoxes of Neoantigens in Predicting Better Prognosis of Cancer Patients

## Abstract

Increased neoantigens of cancer generated by mutations are reported to be associated with favorable prognosis of cancer patients. The interesting findings contradict the notions that cancers were caused by accumulation of gene mutations. The explanation of more efficient immunosurveillance provoked by the neoantigens contributes to the better outcomes also contradicts many more facts, i.e., the immunosurveillance in nature is inflammation which is a term of pathologist. The cancer related inflammation is widely accepted as a cancer promoting fact; more efficient immunosurveillance would result in more apoptosis of cancer cells. However, increased apoptosis were known to be associated with worse prognosis. Moreover, increasing evidence has shown that the expression of immune suppressing genes such as PD-1, PD-L1 and CTLA-4 were associated with better prognosis of cancer patients.

## Dear Editor

The increased neoantigens in the tumor with the prognosis of cancer patients is rather an interesting topic. Recently two papers, one published in Science by McGranahan et al. [1], and an earlier one published in Genome Research by Brown et al. [2], both showed that increased neoantigens generated by gene mutations are associated with favorable outcomes of patients in non-small cell lung cancer, melanoma, colorectal cancer, and tumors from brain, breast, ovaries and kidney. The authors believed that more efficient immunosurveillance targeted at the neoantigens is the underlining mechanism.

However, the story may not be that simple. The findings and their explanation invoke numerous controversies. At first, the somatic mutation theory (SMT) which is the classic, and still the dominant cancer theory today, holds that carcinogenesis is the results of accumulated gene mutations. By inference, more gene mutations should be associated with worse prognosis of cancer patients. The increased neoantigens are generated by more gene mutations. So both the above referred findings are contradicting the SMT theory. This paradox does not mean that the findings of the two papers are not reliable; instead, it detracts scores from the SMT theory, which has encountered fierce criticisms in recent years [3].

Next we see a few more paradoxes from their explanations. Firstly, if increased neoantigens predicts better outcomes due to more efficient immunosurveillance, how could cancer

ever develop? Secondly, increased neoantigens attract more immune cells to the cancer tissue. In pathology, the situation is called inflammation. And it is well accepted that inflammation stimulates cancer development, progression, and metastasis. Notably, the father of cancer immunology ---Dr. Prehn, who first showed convincingly the existence of cancer immunity in 1957, insisted that immune reaction facilitates carcinogenesis and cancer progression, and thus called for suppression of immunity to treat cancer [4,5]. Thirdly, more efficient immunosurveillance caused increased neoantigens should be associated with increased apoptosis in cancer. However, more apoptosis are generally associated with higher malignancy and worse outcomes of cancer patients [6,7]. Pathologists believed that the so-called "resistance to apoptosis" as a hallmark of cancer was a delusion created by molecular biology [7]. Finally, although the inhibition of PD-1 and PD-L1 is now a gold rush in developing the treatment of cancer, increasingly more evidence have shown that increased PD-1 and PD-L1 expression are associated with better prognosis of the cancer patients [8-13], and so is the CTLA-4 [14].

In conclusion, we like the findings of the above discussed papers, but do not think that their explanations could hold up. Accordingly, their calls for stimulation of immune function in the treatment of cancer are also in doubt. We suggest more discussions in cancer theory based on these findings---paradoxes push sciences advance.



## References

1. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, et al. (2016) Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 351:1463-1469. [Link: https://goo.gl/ScLT9L](https://goo.gl/ScLT9L)
2. Brown SD, Warren RL, Gibb EA, Martin SD, Spinelli JJ, et al. (2014) Neoantigens predicted by tumor genome meta-analysis correlate with increased patient survival. *Genome Res* 24: 743-50. [Link: https://goo.gl/UDvxyj](https://goo.gl/UDvxyj)
3. Soto AM, Sonnenschein C (2011) The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory. *Bioessays* 33: 332-340. [Link: https://goo.gl/SBLWH2](https://goo.gl/SBLWH2)
4. Prehn RT (2010) The initial immune reaction to a new tumor antigen is always stimulatory and probably necessary for the tumor's growth. *Clin Dev Immunol* 2010: 851728. [Link: https://goo.gl/WOjZt5](https://goo.gl/WOjZt5)
5. Prehn RT, Prehn LM (2010) Cancer immunotherapy by immunosuppression. *Theor Biol Med Model* 7: 45. [Link: https://goo.gl/B8ayqB](https://goo.gl/B8ayqB)
6. Wang RA, Li QL, Li ZS, Zheng PJ, Zhang HZ, et al. (2013) Apoptosis drives cancer cells proliferate and metastasize. *J Cell Mol Med* 17: 205-211. [Link: https://goo.gl/qvsLLJ](https://goo.gl/qvsLLJ)
7. Wang RA, Li ZS, Yan QG, Bian XW, Ding YQ, et al. (2014) Resistance to apoptosis should not be taken as a hallmark of cancer. *Chin J Cancer* 33: 47-50. [Link: https://goo.gl/hzTsH9](https://goo.gl/hzTsH9)
8. Webb JR, Milne K, Kroeger DR, Nelson BH (2016) PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis in high-grade serous ovarian cancer. *Gynecol Oncol* [Link: https://goo.gl/rLXP2e](https://goo.gl/rLXP2e)
9. Darb-Esfahani S, Kunze CA, Kulbe H, Sehouli J, Wienert S, et al. (2016) Prognostic impact of programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) expression in cancer cells and tumor-infiltrating lymphocytes in ovarian high grade serous carcinoma. *Oncotarget* 7: 1486-1499. [Link: https://goo.gl/ROrlYV](https://goo.gl/ROrlYV)
10. Schmidt LH, Kummel A, Gorlich D, Mohr M, Brockling S, et al. (2015) PD-1 and PD-L1 Expression in NSCLC Indicate a Favorable Prognosis in Defined Subgroups. *PLoS One* 10: e0136023. [Link: https://goo.gl/YXWJgO](https://goo.gl/YXWJgO)
11. Schalper KA, Velcheti V, Carvajal D, Wimberly H, Brown J, et al. (2014) In situ tumor PD-L1 mRNA expression is associated with increased TILs and better outcome in breast carcinomas. *Clin Cancer Res* 20: 2773-2782. [Link: https://goo.gl/7QCwn7](https://goo.gl/7QCwn7)
12. Droeser RA, Hirt C, Viehl CT, Frey DM, Nebiker C, et al. (2013) Clinical impact of programmed cell death ligand 1 expression in colorectal cancer. *Eur J Cancer* 49: 2233-2242. [Link: https://goo.gl/qc85qo](https://goo.gl/qc85qo)
13. Badoual C, Hans S, Merillon N, Van Ryswick C, Ravel P, et al. (2013) PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer. *Cancer Res* 73: 128-138. [Link: https://goo.gl/ujU8UZ](https://goo.gl/ujU8UZ)
14. Yu H, Yang J, Jiao S, Li Y, Zhang W, et al. (2015) Cytotoxic T lymphocyte antigen 4 expression in human breast cancer: implications for prognosis. *Cancer Immunol Immunother* 64: 853-860. [Link: https://goo.gl/QkTj5f](https://goo.gl/QkTj5f)