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Is There Any Genetic Instability in Human Cancer?

Darryl K. Shibata and Michael R. Lieber

USC Norris Cancer Ctr., 1441 Eastlake Ave., MC9176, Los Angeles, CA 90089-9176, (ph. 323 226 7022 dks or 323 865 0568 mrl)

Darryl K. Shibata: dshibata@usc.edu; Michael R. Lieber: lieber@usc.edu

Recent papers in Nature [1,2] reported whole genome sequencing of human cancers. The authors compared the tumor cell line DNA sequence (a melanoma cell line in one case and a small cell lung cancer line in the other) to a nonneoplastic cell line (EBV-transformed peripheral blood lymphoblastoid line) from the same individual. They found about 33,000 genetic changes per genome between the tumor cell line and the nonneoplastic cell line. Initially, one might regard 33,000 changes as a very large number. But simple calculations indicate that human cancer does not appear to manifest an elevated level of mutation over normal cells.

The DNA replication error rate is thought to be $\sim 10^{-9}$ mutations per cell division. The mutations in a tumor (or any cell or cell line) reflect all of the accumulated mutation from the fertilized egg to the inception of the tumor. For dividing tissues, one cell division per day from the point of fertilization to age 55 represents $365 \text{ days} \times 55 \text{ years} \sim 20,000$ cell divisions. Hence, $20,000 \text{ divisions} \times 10^{-9} \text{ mutations per division} \times (3 \times 10^9 \text{ bp/haploid genome}) = 6 \times 10^5$ or 60,000 mutations per haploid genome at middle age. Hence, 60,000 random mutations would be expected in normal cells. In a tumor cell clone, genome sequencing reveals about 33,000 mutations. Therefore, the number of mutations in the tumor (33,000) is no higher than the 60,000 expected, a conclusion also reached with colorectal cancer genome data [3].

The 33,000 mutations per tumor genome represents about 1 mutation per 100,000 base pairs (bp). To put this into perspective, the differences between any two normal human individuals is $\sim 1 \text{ bp per } 1000 \text{ bp}$. Hence, the difference between normal (non-neoplastic) cells of any two individuals is 100 times greater than the difference between a tumor cell and its host.

Given these observations, why do we all have the impression that cancer is associated with a high level of genetic instability? Cancers are associated with changes in chromosome number and chromosome structure. To this extent, there is a genetic instability. However, there has never been any evidence that the number of small insertions/deletions or point mutations was higher than expected for the normal age of the individual with the cancer, and the recent work indicates that the mutation load is indeed no higher than expected based on age.

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What are the implications? First of all, tumors of exactly the same type but from different individuals will have genetic differences that are largely due to the original differences between those two individuals -- not due to the neoplastic transformation. Hence, much of the variation between cancer genomes may reflect that the starting points are so different between individuals. Second, many of the somatic changes in a tumor are likely to largely represent the mutations associated with normal cell divisions that occur during aging of that person before transformation. Because environmental mutational signatures were still evident in the sequenced cell lines, most of the somatic mutations were acquired before tissue culture, as the authors point out [1,2]. Third, because the cancers that arise within a lifetime, by definition, take the fastest pathways, cancer genome data tell us that the most efficient pathways usually proceed with near normal mutation and division rates. The mutations that cause cancer are likely due to a few unlucky critical hits rather than the weight of many changes in aggregate.

References

1. Pleasance ED, Cheetham RK, Stephens PJ, McBride DJ, Humphray SJ, Greenman CD, Varela I, Lin ML, Ordonez GR, Bignell GR, Ye K, Alipaz J, Bauer MJ, Beare D, Butler A, Carter RJ, Chen L, Cox AJ, Edkins S, Kokko-Gonzales PI, Gormley NA, Grocock RJ, Haudenschild CD, Hims MM, James T, Jia M, Kingsbury Z, Leroy C, Marshall J, Menzies A, Mudie LJ, Ning Z, Royce T, Schulz-Trieglaff OB, Spiridou A, Stebbings LA, Szajkowski L, Teague J, Williamson D, Chin L, Ross MT, Campbell PJ, Bentley DR, Futreal PA, Stratton MR. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature*. 2010; 463:191–196. [PubMed: 20016485]
2. Stephens PJ, McBride DJ, Lin ML, Varela I, Pleasance ED, Simpson JT, Stebbings LA, Leroy C, Edkins S, Mudie LJ, Greenman CD, Jia M, Latimer C, Teague JW, Lau KW, Burton J, Quail MA, Swerdlow H, Churcher C, Natrajan R, Sieuwerts AM, Martens JW, Silver DP, Langerod A, Russnes HE, Foekens JA, Reis-Filho JS, van 't Veer L, Richardson AL, Borresen-Dale AL, Campbell PJ, Futreal PA, Stratton MR. Complex landscapes of somatic rearrangement in human breast cancer genomes. *Nature*. 2009; 462:1005–1010. [PubMed: 20033038]
3. Wang T-L, Rago C, Silliman N, Ptak J, Markowitz S, Willson JK, Parmigiani G, Kinzler KW, Vogelstein B, Velculescu VE. Prevalence of somatic alterations in the colorectal cancer cell genome. *Proc. Natl. Acad. Sci. USA*. 2002; 99:3076–3080. [PubMed: 11867767]