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BIOLOGICAL SCIENCES

Confusing cause with effect: the correlation of chromosome Y loss in older men with elevated cancer and mortality risk

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ABSTRACT

Correspondence re: Forsberg, L. A., et al. 2014. "Mosaic loss of chromosome Y in peripheral blood is associated with shorter survival and higher risk of cancer." Nat Genet 46 (6):624-8. doi: 10.1038/ng.2966.

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Forsberg and colleagues found a higher cancer risk in old men who had lost their Y chromosome in some of their white blood cells and hypothesized that Y chromosome loss might be causally involved in carcinogenesis (Forsberg et al. 2014). The authors did not investigate the more probable scenario in which both phenomena (Y loss and cancer) are caused by the same underlying biological mechanism.

In the field of cytogenetics, it has been known for decades that old men sometimes lose the Y chromosome in some of their somatic cells (as old women lose one of their X chromosomes), without any pathological or phenotypic consequences (Stone and Sandberg 1995).

Cancer is mostly an age-related disease, with carcinomas, i.e. malignant epithelial tumors, accounting for 80% of cancer-related deaths in the western world (DePinho 2000). Childhood tumors, sarcomas and leukemias do not show this exponential growth in incidence rates during aging (DePinho 2000), which is suggestive of a different pathological mechanism.

In this short letter, I want to point out that age-associated cancer and age-associated chromosome Y loss might have the same causative mechanism in common, which is replicative telomere erosion in somatic cells. Many decades ago, Barbara McClintock discovered that broken chromosome ends result in breakage-fusion-bridge cycles and chromosomal instability (McClintock 1984). Telomeres are the protective caps of chromosome ends and are known to shorten in somatic tissues during aging (Aubert and Lansdorp 2008). It has been shown that chromosomes with critically short telomeres become unstable and result in numerical and structural chromosome aberrations (der-Sarkissian et al. 2004). Carcinoma cells are characterized by short telomeres and a grossly abnormal chromosome complement, which has been implicated to be causally involved in carcinogenesis (DePinho 2000, DePinho and Polyak 2004).

I therefore suggest that the authors rethink their hypotheses and include telomere erosion as the underlying cause of both phenomena. Accordingly, the observed chromosome Y loss would simply be a biological marker for relatively short telomeres in the somatic tissues of a male individual, which in turn increases the risk for chromosomal instability and subsequently cancer (Stindl 2008). Hence, a reinvestigation of the blood samples with a focus on mean telomere length, using the southern blot technique (Elbers et al. 2014), is highly recommended.

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APPENDIX

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