

## Telomere shortening in childhood versus adulthood: a qualitative disparity

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Sir,

Takubo *et al.*'s interpretation of their study of human liver telomere length (1) perpetuates an error that has for several years hindered progress in understanding the possible role of telomere shortening in aging.

In 1992, Allsopp *et al.* published a seminal study demonstrating the close correlation between telomere length and in vitro replicative potential of primary cultures of dermal fibroblasts (2). They also identified a significant, though weaker, negative correlation between telomere length and donor age, which indicated a shortening of 15bp/year. This value has since been quoted in numerous high-profile publications (e.g. ref. 3).

However, the link between telomere length and replicative potential makes a strong prediction with regard to any relationship to donor age, namely that telomeres of typical tissues will tend to shorten faster during childhood than during adulthood (other things being equal), because their cellularity is increasing during childhood but remains constant thereafter. It is therefore unjustified to draw conclusions about aging from a distribution of telomere length that includes donors under the age of, say, 15. If the "under-age" subset of donors studied by Allsopp *et al.* is excluded, their distribution shows no decrease whatsoever in telomere length with age in dermal fibroblasts. This means, among other things, that the more recent study of Cristofalo *et al.* (4), which reported absolutely no loss of replicative potential with donor age, is not in fact at odds with Allsopp *et al.*'s study, as it has often been portrayed -- and, indeed, as it portrayed itself. (Cristofalo *et al.* also included donors of all ages, but the samples they used only included a very small proportion from such "under-age" donors, insufficient to tug the regression line away from horizontal.)

Takubo *et al.* repeat this error (which plainly applies to hepatocytes just as much as to dermal fibroblasts) when they derive the value of 55bp/year prominently mentioned in their abstract. They acknowledge that there is no *significant* loss of telomere length after the age of 40, but this does not do justice to the data; if we add back the two donors aged 33-39 which their analysis incongruously omits, the already non-significant rate of loss becomes even more negligible. It is thus incorrect to interpret this data as a quantitative change (a slowing of telomere loss) occurring in middle age, as Takubo *et al.* suggest in their closing sentence. Rather, the data imply a qualitative change, from rapid loss to no loss, and the age at which this change happens is not shown to be greater than that at which the liver stops growing. Thus, by far the most economical interpretation of Takubo *et al.*'s data is that loss of telomere length correlates with net rise in cell number of the tissue.

Furthermore, Takubo *et al.*'s depiction of their analysis in Figure 4 compounds the misleading impression given in the text. The choice of 8kb and 11kb as cutoff lengths between different

subsets of telomeres is arbitrary, and inspection of Figure 3 clearly shows that alternative cutoffs (such as 6kb or 12kb) would make Figure 4 imply that telomeres were *longer* after age 80 than in the 40-80 age group. Figure 4 thus constitutes an unacceptably biased summary of the raw data.

The implications of the above points for the role of telomere shortening in liver aging are, needless to say, very different from those that could be drawn from the observation of a slow but non-zero rate of loss during adult life. If average telomere length is constant in a tissue which undergoes cellular turnover (albeit at only a slow rate) but in which no telomerase activity has been found, we must re-evaluate the sensitivity of our telomerase assays and/or the necessity of telomerase for maintaining telomere length in such tissues. Conversely, the rate of decline of minimum (as opposed to average) telomere length appears, from visual inspection of Figure 2, to be considerable; it would be very valuable to know whether it was significant during adulthood (in view of the widely-held and plausible concept that a cell's shortest telomere, not its average telomere, triggers the human cell senescence process), but we are not given this information.

Telomere shortening may or may not play an important role in mammalian aging. We will not easily discover that role unless we maintain a clear picture of what our data truly tell us.

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