OPINION

Comments on "Is telomere shortening reversible? A clue from NASA's twins mission".

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In his "Opinion" article, Vishvkarma addressed the NASA Twin Study findings related to gene expression changes, immune system response, telomere dynamics and other changes in chromosomal inversions and cognitive function. The original study was recently published in Science. Vishvkarma oversimplifies the findings of the NASA Twin Study and inadvertently misleads readers not conversant with the details of that study and its conclusions regarding telomere length alterations. In summary, in this paper we discuss that interpreting the dynamics of astronauts' telomeres is more complicated than addressed by Vishvkarma.

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In his "Opinion" article, Vishvkarma addressed the NASA Twin Study findings related to gene expression changes, immune system response, telomere dynamics and other changes in chromosomal inversions and cognitive function (Vishvkarma 2019). The original study was recently published in Science (Garrett-Bakelman et al. 2019). Vishvkarma oversimplifies the findings of the NASA Twin Study and inadvertently misleads readers not conversant with the details of that study and its conclusions regarding telomere length alterations.

The original paper published in Science clearly states "Most notable was a significant increase in telomere length during flight for TW (14.5%), as compared with his preflight and postflight measures as well as with those of HR (P = 0.048, 0.0003, and 0.0073, respectively; one-way ANOVA). TW's increased telomere length was observed at all inflight time points assessed [flight day (FD) 14 to FD334; fig. S6A], as well as in sorted CD4, CD8, and LD cells, but not in CD19 cells (Fig. 2B and fig. S6B). These results are consistent with recently reported cell type–specific responses to factors that contribute to telomere length regulation (22). Notably, telomere length shortened rapidly upon TW's return to Earth, within ~48 hours [FD340 ambient return to R+0 (R+ days post return); fig. S6B] and stabilized to near preflight averages within months".

Figure 1 of Vishvkarma's paper illustrates an exaggerated telomere shortening after returning to Earth with the occurrence of normal length after 6 months. These observations are inconsistent with Figure 2 (B) of the original article. Figure 2 (B) shows that for CD8 the post-flight telomere length is much longer than the pre-flight value. Moreover, CD4 and LD almost show returning to pre-flight telomere length. Therefore, CD19s are the only PBMC subpopulations that show a post-flight shortened telomere length compared to the pre-flight value.

Vishvkarma has not fully evaluated the key role of space stressors (e.g. radiation and microgravity) in the telomere dynamic. A key question about the elongation of Scott Kelly's telomeres during space flight is whether we can interpret it a positive (adaptive) response to multiple changes in the environment (e.g. higher levels of radiation or microgravity)? A simple response can be "yes", something like constriction of our pupils when we move from a too dark place to a too bright place. This side of the coin (adaptation to stressors and longevity) seems to be very positive. The importance of adaptive responses in space missions has been previously addressed (Mortazavi et al. 2003, Bevelacqua and Mortazavi 2017, Bevelacqua et al. 2018). However, it should be noted that elongation of telomeres by telomerase activity is a phenomenon which extends the life of cancer cells. Therefore, appropriately addressing the following points seems necessary:

1) Telomerase activity is observed in about 90 % of human cancers and cell lines (Kim et al. 1994) while normal human cells including stem cells have lower telomerase activity (Jafri et al. 2016).

2) Telomerase inhibition is a promising strategy for cancer treatment(Holysz et al. 2013).

Accordingly, any stressor-induced telomerase activity in space would be a double-edged sword with both favorable and unfavorable consequences! There is increasing evidence that many people (almost all) develop covert cancer (Greaves 2014). However, as long as someone has an actively functioning immune system, these cells cannot proliferate and there is no extensive development of the cancer cells. Moreover, in a long-term space mission, development of cancer in astronauts who are 40 years old or older, is potentially more likely as their immune systems degrade. Scott Kelly, the only NASA astronaut who spent nearly a year on the International Space Station, was born in 1964 and represents a

member of this age cohort. Given these considerations, interpreting the dynamics of astronauts' telomeres is more complicated than discussed by Vishvkarma.

Conflict of Interest

Authors declare no competing interests.

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