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Commentary

Cellular Senescence and Inflammatory Burden as Determinants of Mortality in Elderly People Until the Extreme old age

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Human aging is accompanied by a chronic low-grade inflammation, called "inflammaging", a phenomenon associated with frailty, morbidity, and mortality in elderly people (Franceschi and Campisi, 2014). This condition is related to the accumulation of senescent cells in aged tissues through the senescence-associated secretory phenotype (SASP), which includes pro-inflammatory cytokines among its key constituents (Franceschi and Campisi, 2014).

A well-known trigger of cellular senescence, closely related to inflammaging, is telomere length shortening. However, while considerable evidence shows that circulating inflammatory markers are predictors of mortality in community-living elderly individuals (Giovannini et al., 2011; Varadhan et al., 2014), there are conflicting results on the role of telomere length (Deelen et al., 2014; Bendix et al., 2014).

Arai et al. (2015) in this issue of *EbioMedicine* demonstrate with a cross-sectional approach that telomere length, measured in the DNA extracted from whole blood of centenarian offspring, centenarians and (semi-)supercentenarians displays a superior maintenance compared to the one measured in community-living elderly subjects. Indeed, telomere length of centenarian offspring is maintained for more than 20 years at a length corresponding to 60 years of age in the general population. Interestingly, the authors observed that while long telomeres might be a prerequisite for exceptional lifespan in humans, they did not predict mortality. Conversely, Arai et al. confirmed that a multibiomarker score of systemic inflammation, which included anti-cytomegalovirus IgG, IL-6, TNF-α and C-reactive protein levels, was associated with an increased risk of mortality, loss of cognitive function and physical function decline, in normal aging and at extreme old age (up to 110 years).

These data demonstrate that a multiple biomarker index may represent a more powerful predictor of mortality in older adults than a single inflammatory mediator, as also recently shown through a combined measure of interleukin 6 (IL-6) and soluble TNF receptor 1 (sTNFR1) (Varadhan et al., 2014).

Therefore, the development of reliable measures of inflammatory status is of great interest in clinical practice both as risk assessment tools of age-related chronic diseases, and to monitor clinical progression or as a powerful surrogate biomarker in the research of new anti-inflammatory therapeutics.

Hence, given that inflammation is a consolidated predictor of mortality, it is also important to investigate the sources of this phenomenon and their relative contribution. While it is known that cell senescence and inflammation can drive each other thus causing accelerated aging, the results of Arai and co-workers suggest that blood telomere length might not reflect the phenomenon of accumulation of senescent cells in various tissues and organs. This could be particularly true if accumulating senescent cells will be confirmed as a major source of circulating inflammatory markers in aging.

The finding regarding the clearance of p16Ink4a-positive senescent cells which delay aging-associated disorders in genetically engineered mice (Baker et al., 2011) opens interesting future perspectives regarding therapeutic approaches aimed at the removal of senescent cells to prevent or delay tissue dysfunction and extend healthspan. However, senescent cells may also exert a physiological role as demonstrated for wound healing (Demaria et al., 2014) and their clearance could have adverse outcomes, especially in young organisms. For these reasons it is necessary to intensify the research effort in order to clarify the effects of the selective elimination of senescent damaged cells in aged animal models.

In this context, the development of strategies to remove senescent cells could represent an emerging tool for the suppression of chronic inflammation and to ameliorate human healthy lifespan. A feasible and suggestive approach may be the employment of senolytic compounds (Zhu et al., 2015), in particular natural bioactive compounds, such as quercetin, which might be easily used in clinical trials, while minimizing the risk of adverse events (Malavolta et al., 2015).

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Conflict of Interest

The authors declare no conflicts of interest.

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