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Greater organ involution in highly proliferative tissues associated with the early onset and acceleration of ageing in humans

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ABSTRACT

Domination of cell proliferation over cell death is a driving force for carcinogenesis, whereas reduced cell proliferation and increased cell death are characteristic of ageing. We employed published data to estimate representative mean values of cell turnover times for 31 different organs and tissues in adult humans and animals (when data in humans were lacking) as well as functional mass loss for 5 organs, accounting for actual mass loss and tissue conversion to fat, in humans over the adult period, age 25 to 70. We found that greater actual and functional mass loss was significantly associated ($P = 0.001$ and $P < 0.0001$, respectively) with the log of shorter cell turnover times. We propose that this is characteristic of stem cell exhaustion and replicative senescence. In addition, we provide quantitative evidence that, in many organs, involution is evident even in young adults. On the basis of published mass measurements of major organs, by analysis of covariance, we identified examples of significant ($P \leq 0.05$), accelerated actual or functional mass loss and ageing from early to late adulthood. We hypothesise and quantitatively demonstrate that functional mass loss accelerates with ageing by incorporating the contribution of actual mass loss, tissue conversion to fatty or fibrous tissue, and the presence of apoptotic, necrotic and senescent cells. We propose that mass loss, linked to replicative senescence, is an evolutionary adaptation that effectively limits cancer in young adults, as mass loss is first apparent soon after the end of the growth period, accelerating in the more elderly as biological conditions deviate away from those prevailing in youth, when the selective pressure on pleiotropic genes is greatest.

1. Introduction

Progressive atrophy or involution accompanies ageing and is characterised by common conditions including Alzheimer disease (Burns et al., 2010), sarcopenia and osteoporosis. During the age-related involution of organs and tissues (hereinafter "organs" for brevity), functional or fundamental tissue integrity is reduced, chiefly by one of four means: first, mass loss due to lack of replacement of cells after apoptosis, necrosis, mitotic catastrophe and perhaps autophagic cell death; second, irreversible cellular senescence; third, inflammatory cell infiltration; and fourth, conversion of a functional tissue to another form, such as fatty or fibrous tissue. Conversion to fat occurs in most organs, but particularly in the bone marrow, breast, muscle, pancreas and thymus. Both fibrous material and fatty infiltrates are associated with chronic inflammation, a biomarker of ageing (Chung et al., 2009; Richardson, 2011b; Schaffler et al., 2006).

Multiple interwoven mechanisms promote age-related involution, including increased oxidative stress levels, loss of sex hormones, insulin resistance (e.g., fatty liver disease), lowered production of growth hormone, and tissue energy metabolism (Almeida et al., 2007; Krems et al., 2005). In the case of sex steroids (hormones), their loss due to gonadectomy or ageing is associated with involution of reproductive organs, osteoporosis and cognitive decline (Lin et al., 2011).

Shorter cell turnover times (i.e., average renewal time of a cell population) have been shown to be associated with an elevated tumour incidence in selected tissues in both humans and rodents (Baserga and Wiebel, 1969). The predominant cell populations in many organs are epithelial and stromal cells. In general, epithelial cells have a far higher turnover and cancer incidence than other types of cells, accounting for 80% of all human cancers. For example, for cells in the jejunum, the average age of all cells has been calculated at ~10.7 years. However, the cell replacement time varies from ~5 d for epithelial cells to 15.9 years for stromal cells (Spalding et al., 2005). The rapid-turnover epithelial cells give rise to adenocarcinoma, the most common cancer of the small intestine, while from the stromal cells rarer sarcomas originate.

While several qualitative reports have examined the relationship between cell proliferation and cell death in a specific tissue, a quantitative study of multiple organs is lacking. To advance our understanding of

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ageing-related cellular processes that contribute to carcinogenesis, we investigated whether mass loss in a variety of organs was associated with cell turnover times for these organs. Furthermore, we determined the age at which organ mass peaks or plateaus, the age after which mass loss begins, and whether mass loss accelerates over adult life. Therefore, we systematically reviewed published studies of cell turnover time and organ mass loss, and analysed data from these studies to determine changes in the rate of mass loss between early and late adulthood. We then examined our results to discuss whether the relationships found support current theories of the effects of radiation and of normal ageing.

2. Materials and methods

2.1. Cell turnover time and organ mass loss

We searched the published literature for reported cell turnover times for various whole organs and tissues, or for their major and most rapidly replaced cell component. Data in humans were preferentially selected where available; in the absence of data in humans, we used data from rats or, if there were no data from rats, from mice. As organ turnover times vary with age, those tabulated were of younger, rather than older, adults. When turnover times were not available, they were estimated as the reciprocal of the fractional turnover rate (fraction per day) or from half-life (day) data by dividing by the natural logarithm of 2.

Reported turnover times for different parts of the respiratory tract, dominated by endothelial cells, are particularly divergent. The bronchioles, alveolar ducts and sacs, rather than the tracheobronchial tree, make up the major part (>90%) of the lung mass. No estimate was found of the turnover time for Type I epithelial cells, which constitute >95% of the alveolus surface. The turnover time of 200 d for the bronchioles of rats by Blenkinsopp (1967) was selected as the representative value, although an even slower proliferation was measured by Rawlins and Hogan (2008) for bronchioles in mice (mean half-life 470 d).

As well, we searched for publications reporting the change in "actual" organ mass in adults from the age of 25 to 70 years, or as close to those years as possible. For example, organ mass for adults 25 years old were evaluated in some instances as the mean of two reported values for 20–24 and 25–29 years old. An allowance was made for small (within 5 years) deviations from the 45-year range (e.g., Dekaban and Sadowsky, 1978 reported results for ages 20–30 years to 70–80 years). The upper age range was limited to 70 years of age principally owing to a paucity of data beyond this age. For the bone marrow (Bain et al., 2010; Richardson and Dubeau, 2003), breast, muscle (Marcus et al., 2010), pancreas (Saisho et al., 2007) and thymus (Steinmann et al., 1985), we went some way to estimating functional mass loss by reducing the actual mass due to tissue conversion to fat. For the breast, the functional mass change from 25 to 70 years was evaluated as the decrease in non-fat tissue (collagen/fibrous and glandular) by 31% and 38% from the mammographic density studies by El-Bastawissi et al. (2000) and Li et al. (2005), respectively. Using the data of El-Bastawissi et al. (2000), the mid-range values for the non-fat tissue of four age groups was derived from four breast density ratings. Using the data of Li et al. (2005), the difference in the non-fat tissue of two age groups, mean ages 33 and 64 years, was linearly extrapolated to a 45-year range.

Linear correlation analysis was carried out to determine the strength of the relationship between organ turnover times and mass loss. Organs were excluded from the analysis if data regarding cell turnover times or mass changes with ageing were lacking, or if the representative cell type most rapidly replaced constituted ≤10% of the organ volume.

2.2. Mass loss onset and acceleration

The age at onset of mass loss was identified as occurring after peak mass, and specifically as the age or mid-range age that mass loss begins and continues with age. Organ mass loss onset and acceleration with ageing for most organs was analysed employing the published data in six different examinations, described below. For the remaining organs, the age at onset of mass loss was estimated on the basis of previously published studies (Table 1). Lastly, for all organs exhibiting continuous mass loss (defined as continuous loss except for one time point) with ageing, the age at onset for each organ was estimated by selecting the mid-point of an age range and averaging by laterality and sex, where appropriate. Further, the acceleration of mass loss during early and late age periods was calculated in the last three examinations. Slopes from regression analyses of mass change rates between the early and late age periods were statistically compared by analysis of covariance (ANCOVA).

First, we examined the constant mass loss rate of four organs during adulthood by linear regression analysis using autopsy data provided by He et al. (2009).

Second, age-dependent bone marrow mass was estimated, taking into account skeletal growth, bone marrow cellularity, and apoptotic cells (Bain et al., 2010; Richardson and Dubeau, 2003). Apoptotic cell data was interpolated and extrapolated from 6.5, 7.2 and 19.6% of human bone marrow cells exhibiting apoptosis at 10, 55 and 90 years of age, respectively (Ogawa et al., 2000).

Third, the age-dependent analysis of three female sex/reproductive organs were individually estimated from one published study if the age range of the data was adequate, or two separate studies if not. Representative parameter values of mass loss onset were estimated from data for breast tissue conversion to fat (Boyd et al., 2010), ovary volume (Cohen et al., 1990), and endometrial thickness (Amir et al., 2007; Gurbuz et al., 2004).

Fourth, for six organs we used autopsy data by Ogiu et al. (1997), for age points t_i, (yearly until age 19 years, midranges of five-year periods for >19 years and a ten-year period, 85–95 years). We calculated the rate of actual mass change by a three-time-point (t_{i-1}, t_i, t_{i+1}) moving-window, linear regression analysis. The onset age t_i of mass loss was then conservatively identified as the age when the rate became consistently negative (one point exception allowed) from that age onwards. Linear regression analyses were carried out for an early period starting at onset age of mass loss (e.g., 22–52 years), followed by a late period with a generally similar number of age points (e.g., 57–90 years old). The same analysis was applied to the functional pancreatic mass values (not tabulated). The adrenals, heart, thymus and thyroid were excluded from the analysis of data by Ogiu et al. (1997) due to lack of consistency in mass loss rate in adulthood.

Fifth, the functional mass loss (equivalent to functional volume loss assuming 1 $g \cdot cm^{-3}$) of the thymus was estimated from the data of Steinmann et al. (1985) for mid-range ages by evaluating the functional thymic volume as comprising the thymic epithelial space and lymphocytic perivascular space.

Sixth, changes in the actual body cell mass, and actual and functional skeletal muscle mass, were based on Kyle et al. (2001), which reported regression analyses for data divided into two age groups (17–59 years old and 60–94 years old). Comparison of early and late mass rates was carried out on data acquired by digitizing the relevant published figures. Onset of mass loss was evaluated from the mean mass of decadal age groups.

3. Results

3.1. Cell turnover time and organ mass loss

We examined reports of 31 organs or their major cell types (Table 1). Cell turnover times for the organs or their cell types had a very wide range, from 1.4 to 25 300 d (Table 1, Fig. 1A and B). The gastrointestinal tract, thymus and bone marrow were found to have high cellular turnover, whereas the heart, brain, bone, and muscle have low turnover and regenerative capacity. For consistency, we report cellular turnover times in young adults, where possible, as evidence shows that turnover

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