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Brief Communication

Parental telomeres implications on immune senescence of newborns

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Abstract: Telomere, the biological chronometer, and its effect on the immune system considerably varies among individuals. During pregnancy, multiple risk factors affect telomere reprogramming during fetal life which can lead to health disparities in newborns. These changes may cause a long-term impact on the telomere genetics of the newborn and become a reason for lifelong health implications and immune senescence. Therefore, telomere shortening in parents due to genetic variation may act as a hallmark of immune senescence and aging in their newborns.

Keywords: Telomere, immune senescence, telomerase, newborn

Introduction

Immunity maintains tissue homeostasis, but with time the age-related functional decline of responses may cause immune senescence. Immune senescence is accompanied by variations in immune response in the body that may lead to increased inflammatory mediators that affect neighboring cells and telomeres [1]. This makes the body sensitive to inflammatory disorders and infectious diseases. Moreover, it is a multifactorial response, dependent on the environmental changes, antigenic reactions, and epigenetic modifications that ultimately form the immunobiography of an individual (**Figure 1**).

Telomeres

Telomeres, play a critical role in genomic stability and have long non-coding ribonucleoprotein with tandem repeat (approximately 300-8000) sequences (TTAGGG) at the end of the chromosome [2]. During every cell division, telomeres shorten (30 to 200 base pairs) in somatic cells rather than germ cells, stem cells and cancerous cells. p53 protein recognizes the Hayflick limit (extremely shortened telomeres) of the telomere, it activates replicative senescence of cells along with cellular apoptosis and telomeropathies like cardiovascular disease [3], metabolic disease [4], upper respiratory track diseases in children [5] and chronic obstructive pulmonary disease (COPD) [6]. On the contrary, longer telomeres due to enzyme telomerase increased the risk of different cancers [6-12].

Factors affecting telomeres

Multiple studies have reported that leukocyte telomere length (LTL) is multifactorial and has been affected by age, gender, Body Mass Index (BMI), hormone (higher estrogen), physical inactivity, smoking, alcohol intake, stress, antioxidants, vitamins (folate, nicotinamide, vitamin A, B12, C, D, and E), trace and toxic elements (magnesium, zinc and iron), inflammation, paternal age and most importantly socioeconomic status (SES) of parents [13].

According to literature, different viral studies revealed that infections like human immunodeficiency virus (HIV), and nowadays pandemic COVID-19 trigger extensive proliferation of T cells and lymphocytes with short telomeres [14, 15].

Earlier in 2019, we published the data on genetic programming in fetus irrespective of SES. It was found that smaller telomeres (T/S ratio: 1.13 ± 0.18, 6432 ± 1350 base pairs) in mothers compared to newborns (cord blood)

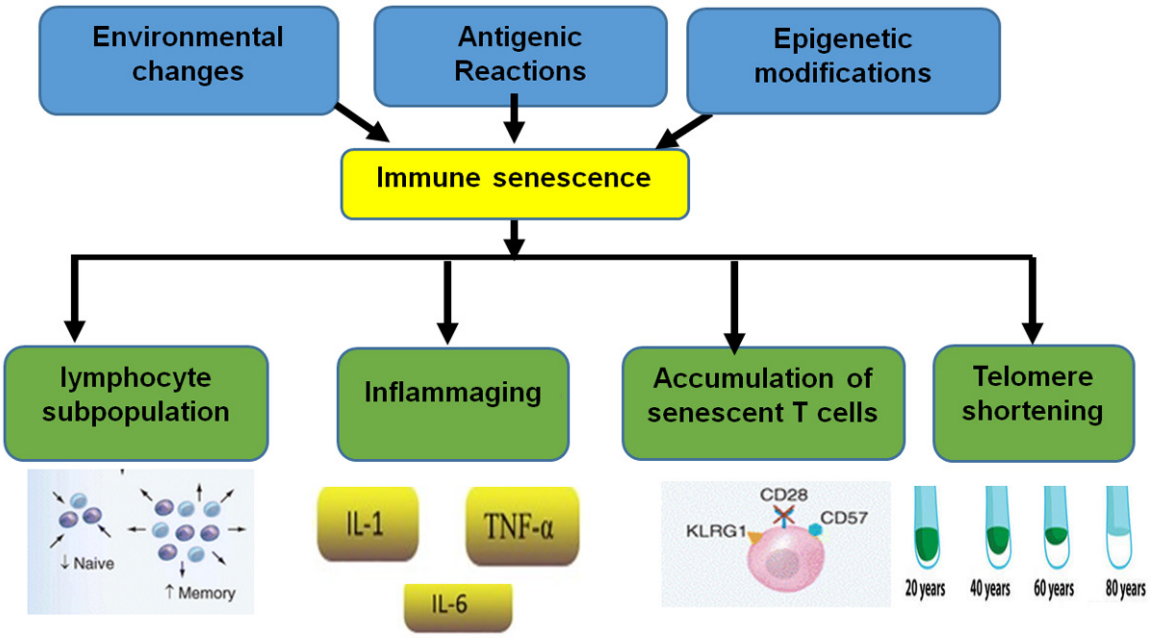

Figure 1. Immune senescence in the human body. Immune senescence is a multifactorial response, and results in different reactions in the body which may ultimately lead to telomere damage.

(T/S artio: 1.18 ± 0.23, 6765 ± 1350 base pairs). Our results also highlighted that high SES mother-cord base pairs (6818 ± 1248-6936 ± 1326) had longer telomeres than low SES (5916 ± 754-6214 ± 596) which confirmed that there is telomere reprogramming during fetus life [16, 17]. Thus above literature emphasizes the role of maternal telomeres and their transfer to newborns. Therefore, it was observed that there is a research gap in the detection of inheritance patterns of telomeres from either mother or father. Such changes in telomere may lead to immune senescence or premature aging in newborns, especially among social disparities.

Immune senescence

Immune aging is a complex and diversified area of research, certain T cells can be evaluated by different markers like CD27 (co-stimulatory immune checkpoint), CD28 (co-stimulatory signals), CD45 (leukocyte common antigen), CD57 (sulfated glycan carbohydrate on chronic immune activation T cells) and Killer cell lectin-like receptor subfamily G (KLRG1) (co-inhibitory or immune checkpoint) [1]. KLRG1 acts as a key immune senescence marker which acts as an inhibiter for NK and T cells. It has an immunoreceptor (tyrosine-based inhibitory motif) in its cytoplasmic domain. If KLRG1 is prohibited to ligate on T cells it increases AKT phosphorylation which boosts the cell proliferation capacity and improves the action of cell cycle proteins, cyclin D, cyclin E, and a reduction of cyclin inhibitor p27. On the other hand, CD57 is a glycoepitope, but its ligand remains unknown, a proliferation of T cells expressing CD57 is severely increased with aging [18].

Research also highlighted that the loss of surface markers CD27 and CD28 on the immune cells will upregulate p16 and p21 of cell cycle regulatory proteins and may induce p53 under stress, and is more related to senescence due to telomere damage [18]. Therefore, the shortening of telomeres can act as a hallmark of senescent T cells. This may be due to T cells' continuous replication and a TERC gene expression reduction, which ultimately affect telomerase activity. Later on, it was discovered that loss of CD27 and CD28 expression could be associated with a reduction of telomerase activity or vice versa [19]. Senescent T cells are also prolific producers of different cytokines, IL-6, IL-8, IL-10, TNF, IFNγ, and TGF-β but they fail to proliferate effectively when stimulated. Hence, senescent T cells, which lost their replicative capacity, show CD27 and CD28 down-

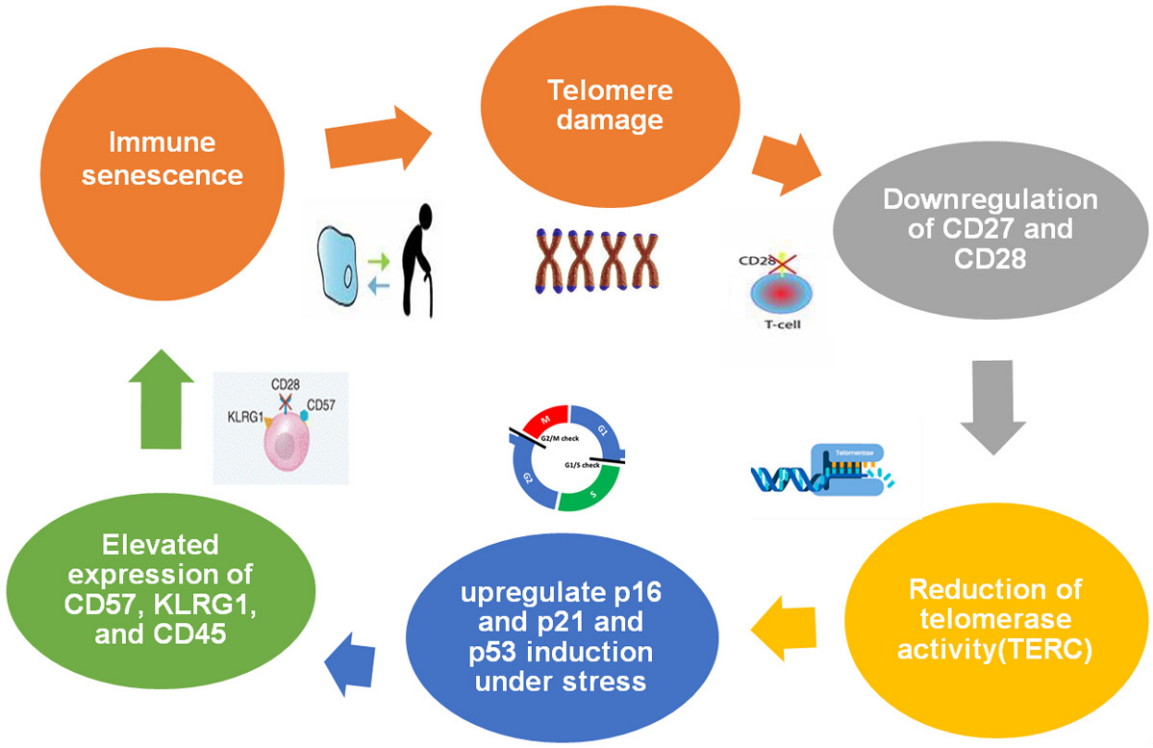

Figure 2. Immune senescence due to telomere damage. Telomere damage may cause due to the downregulation of CD27 and CD28 and reduction of telomerase activity or vice versa on the immune cells which may lead to upregulation of p16 and p21. Therefore, senescent T cells lost their replicative capacity and increase expression of CD57, KLRG-1, and CD45 immune markers.

regulation and elevated expression of CD57, KLRG-1, and CD45 [19] (**Figure 2**).

Telomere, telomerase and immune senescence

Along with telomeres, telomerase activity increases during the earlier gestation period but after birth, telomeres are gradually shortened with age. Stress exposures in mothers, metabolic or endocrine disturbances, or oxidative, immune systems, can alter the telomere biology which may lead to cellular and immune senescence. Immune senescence owing to telomere attrition includes loss of T cells (naïve T cells), increase in reserves of memory T cells along with interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). Both IL-6 and TNF-α upsurge telomerase activity by activation of NF-κB, STAT1, and STAT2 pathways. However, the mechanism causing aging by such mediators of inflammation is still under investigation. Additionally, immune senescence driven by inflammation is called "Inflammaging" which can distinguish between the pathological and natural age-related accumulation of Reactive oxygen species (ROS), and may prime oxidative stress, mitochondrial dysfunction, and release of DNA into the cytosol especially in neutrophils [20].

Telomerase genes (TERC and TERT) and telomere

Many Genome-wide association studies (GWAS) have mixed results in evaluating the possible impact of human TERC and TERT gene polymorphisms on telomere length and its association with common diseases, aging, and lifespan. Previously a GWAS of European descent identified SNPs in 7 loci from which 5 loci (*TERC, TERT, NAF1, OBFC1, RTEL1*) were identified in telomere biology but lead SNPs (*TERC* and *TERT*) associated with different diseases and cancers [21]. To date, data from large-scale populations have also illuminated many SNP's roles in human telomere homeostasis and their association with different diseases like respiratory diseases, acute myeloid leukemia (AML), gastric, lung, and hepatocellular cancer [6-12].

A study on maternal-newborn samples found that both the TERC and TERT were associated with shorter telomere length (P = 0.041 and 0.046, respectively) [22] and can be considered as the potential functional genes in the alteration of telomere genetics [23].

In 2020 a study used "teloscore" by weighing the effect of each single nucleotide polymorphism (SNP) on LTL, based on the knowledge of the allele associated with LTL increase. So "genetically determined" telomere length by teloscore was used to identify the telomere length [24].

A genetic analysis, in Singaporean Chinese population highlighted 10 genome-wide loci associated with telomere gene (TERC and TERT) SNPs, respiratory infections and immunological competence [7]. Moreover, an increased hTERT expression and shorter telomeres were linked to the development of gastric cancer and its progression and its relationship with numerous etiological risk factors and transcriptional activators [25].

The current knowledge about telomeres and telomerase reiterates the importance that should be also devoted to monitoring lifestyle and health-promoting measures, social and clinical factors, that may increase telomere length and immune senescence of the cells which can help in balancing various cellular functions and preventing multiple diseases.

Now point to ponder is that there is a dire need for the identification of parents and newborn connection in telomere genetics by genetic screening of newborns which can spotlight clinical risks in newborns. Similarly, different clinical risk factors may also affect parents' immune senescence that can be inherited to their newborn. As the world is approaching precision medicine, such basic research on chromosome stability and genetic screening may become a part of antenatal care, which can help in designing directed therapies for disorders at hand in the near future.

Statement of significance

Looking into the telomere length by working on the telomere maintenance genes (TERC and TERT) and their single nucleotide polymorphism (SNP) and its association with immune senescence may be significant for the identification of inheritance patterns. The telomere changes identification from either father or mother, highlights the risk of different clinical factors in parents-newborns, due to telomere length variation. Therefore, such research on immune senescence and its association with telomere genetic variation should be a priority agenda for research-based organizations and public health policymakers.

Conclusion

The studies regarding telomeres should not only be confined to aging but also give an insight into genetic variations of telomere maintenance gene and telomere length association with immune scenesense. Such studies can instigate public health awareness and intimating health significance among the local population.

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Disclosure of conflict of interest

None.

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