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The Future of Onco-Cardiology: We Are Not Just "Side Effect Hunters"

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Abstract

Cancer treatments in general share various detrimental effects in common, especially upregulation of cardiovascular risk factors. Therefore, the science of onco-cardiology should not be restricted in scope to the side effects of each specific cancer drug. In particular, premature aging induced by cancer treatment may contribute to the chronic health problems of cancer survivors.

Keywords

onco-cardiology; premature aging; shelterin complex; telomere shortening; cancer survivors

Introduction

About 1,660,000 people, including more than 12,000 children under the age of 18, are newly diagnosed with a malignancy in the USA every year.[1] The American Cancer Society reported that in 2016 there are 15.5 million cancer survivors in the USA (http://www.cancer.org/cancer/news/news/report-number-of-cancer-survivors-continues-to-grow). At present, the 5-year survival rate of patients treated for cancer is 67%. Seventy-five percent of children in whom cancer is diagnosed today will live for at least 10 years; 20% will survive for longer than 35 years.[1] Although these numbers are impressive compared with those from decades ago, further improvement of cancer survivors' life span as well as quality of life and functional status is still necessary.

Approximately 75% of cancer survivors have some form of chronic health problem. Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in this population, particularly after recurrent or second malignancy. The risk of CVD in cancer survivors is 8 times higher than that of the general population. The relative risks of coronary artery disease and heart failure in cancer survivors are 10 times and 15 times higher, respectively, than their siblings without cancer.[1] Cancer treatments, including chemotherapy and radiation, can lead to both short- and long-term cardiovascular complications. Evidence

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of subclinical cardiac and vascular damage was observed in more than 50% of survivors 5 to 10 years after chemotherapy.[1]

Onco-cardiology: focus on cardiovascular effects of cancer and its treatment

Onco-cardiology is a medical subspecialty concerned with the diagnosis and treatment of CVDs and organ failure mediated by microcirculatory or macrocirculatory defects in cancer patients. Although identifying the cardiovascular side effects of emerging cancer therapies is critical, the key goal of onco-cardiology is to allow patients to receive maximum and uninterrupted treatment for cancer while protecting them from cardiovascular complications mediated by this treatment. The onco-cardiologist must understand not only the pathophysiology of CVDs but also the mechanisms through which each cancer treatment controls cancer growth and metastasis. Armed with this profound knowledge of the pathophysiological, clinical, and epidemiologic aspects of the cardiovascular complications of cancer therapies, we can establish strong, evidence-based strategies for managing both short-term and long-term cardiovascular complications after treatment.

Two major approaches have been taken in the field of onco-cardiology research. The first considers cardiovascular disease in cancer survivors as a side effect of cancer treatment and determines the unique molecular mechanism induced by each treatment. For example, topoisomerase-IIβ (top2β) is reported to be one of the direct target molecules of cardiotoxic drugs of the anthracycline family[2]. Thus, depletion of top2β ameliorates anthracycline-mediated cardiotoxicity. Notably, since heart only expresses top2β, new anthracycline that only poisons top2α, but not top2β, will be beneficial for healing cancer, but avoiding cardiomyopathy. Many new anticancer drugs are designed to target specific intracellular signaling pathways to control tumor progression, and many have unexpected cardiovascular effects. These unintended discoveries can provide unique insights into human cardiovascular biology.

The second approach of onco-cardiology takes advantage of these unexpected findings and applies them to the study of the cardiovascular system. For example, a number of cancer therapies targeting novel kinases, including tyrosine kinases, are being developed. Some of these drugs can affect the cardiovascular system in detrimental ways, while others can be beneficial.[3]

Both approaches rely on the specificity of each cancer drug and help us to determine and understand the unique and critical cardiovascular and cardio-metabolic pathways for maintaining the function of both heart and vasculature.

Upregulation of cardiovascular risk factors in cancer

Although these approaches greatly inform investigation of the mechanisms underlying CVD in cancer survivors, we believe that onco-cardiology should not be restricted so narrowly. While understanding the side effects of each specific cancer drug is valuable, many cardiovascular phenotypes have been identified as common across different cancer

treatments. For example, Lipshultz *et al.* reported that cancer survivors show pathological cardiovascular phenotypes even without exposure to a cardiotoxic treatment. They showed that both survivors who have and those who have not been treated with a cardiotoxic drug exhibit lower left ventricular mass and more cardiac dysfunction than siblings without cancer. In addition, both exposed and unexposed survivors had a higher mean body mass index and higher levels of fasting serum HDL cholesterol, insulin, and high-sensitivity C-reactive protein than cancer-free siblings. This suggests that all cancer survivors, regardless of exposure to cardiotoxic treatments, have a higher-than-expected risk of CVD.[4]

In the St. Jude Lifetime Cohort study, 98% of 1,713 adult survivors of childhood cancer (median age 32 years, range 18-60) had at least one chronic health condition; by age 45, the estimated prevalence of a serious, disabling, or life-threatening condition was 80.5%. Interestingly, the prevalence of risk factors for CVD—including hypertension, dyslipidemia, and obesity—in this group was high (22.6%, 50.9%, and 36.5%, respectively), but high-risk treatments (as defined by Children's Oncology Group guidelines) contributed little to the occurrence of these risk factors.[5] Taken together, these data suggest that cancer treatments have some detrimental effects in common, particularly the upregulation of cardiovascular risk factors.

Many cancer treatments can cause apoptosis of cardiomyocytes and damage the remaining cardiomyocytes and progenitor cells. Since cardiomyocytes do not replicate easily, it is understandable that the effects of cancer therapy on the heart last for an extended period of time. However, vascular cells—including endothelial cells, smooth muscle cells, and macrophages—can replicate and renew themselves easily. Therefore, it is difficult to understand how the relatively short-term insults given by cancer treatments show significant vascular effects and upregulate cardiovascular events for a long period of time after cancer treatment.

Accelerated cellular senescence key to increased CVD risk in cancer survivors

In the St. Jude Lifetime study cohort, childhood cancer survivors showed an extraordinarily high prevalence of chronic health conditions of the lungs, heart, and brain. The authors of the report suggest that premature aging induced by cancer treatment may contribute to the chronic health problems in cancer survivors.[5] How this premature aging process is induced by cancer treatments and persists for a long time post-treatment remains unclear. It is well known that one of the common features of radiation therapy is the shortening of telomeres, which is also closely related to aging. This telomere shortening has a significant impact on CVD. We propose that many of the long-term detrimental effects of cancer therapy are caused by telomere shortening and dysfunction.

Accelerated cellular senescence is a common denominator that could affect several cell types that are relevant to atherosclerosis. Cellular aging can be thought of as a progressive decrease in cells' ability to cope with various stresses that may induce chronic pathological conditions, including CVD. Telomeres are specialized protective caps at the end of chromosomes, consisting of a DNA-protein complex that prevents recognition of natural

chromosome ends as DNA double strand breaks, thereby preventing degradation. They play an important role in cellular senescence. Telomerase is a telomerase-lengthening enzyme. When a telomere becomes dysfunctional because of shortening or loss of protective factors, chromosome ends activate a DNA damage response (DDR) mediated in part by H2A histone family member X (γ-H2AX). It is well known that in patients with dyskeratosis congenita, or premature aging syndrome, manifestation of aging phenotypes such as liver fibrosis, idiopathic pulmonary fibrosis, and bone marrow failure depends on the degree of telomere shortening and dysfunction.[6] Moreover, premature aging mouse models of Werner syndrome and ataxia telangiectasia develop classical human-like aging pathologies only when their telomeres are shortened.[7] These studies demonstrate the essential role of short telomeres in premature aging diseases. Telomere shortening in endothelial cells has also been tied to aging and atherosclerosis.[8]

How telomere shortening and dysfunction result in such widespread body degeneration typical to aging has been widely studied, but to precisely understand this process, we need to rethink what the process of “aging” is. In addition to telomere shortening, the following four events have been described as aging phenotypes: DNA damage and apoptosis, excess inflammation, mitochondrial dysfunction, and reactive oxygen species (ROS) production.[9] Telomere shortening can explain the induction of all these aging phenotypes (Fig). First, it has been reported that the presence of a few dysfunctional telomeres may be sufficient to trigger DDR following DNA damage,[10] and p53 expression induced by DDR associates with the promoters of PPARγ co-activator 1-alpha (PGC1α) and PGC1β to repress expression of those genes, leading to inhibition of mitochondrial biogenesis and function and upregulation of ROS. Passos *et al*. reported that mitochondrial dysfunction and ROS production not only accelerate the onset of senescence by enhancing telomere dysfunction, but also are consequences of telomere dysfunction. This positive feedback loop between ROS and telomere dysfunction maintains DDR signaling via the p53-p21-TGFβ pathway (Fig).[11] Finally, the crucial role of ROS production in regulating inflammation is well established. Taken together, these data strongly support the essential role of telomere dysfunction in inducing a variety of aging phenotypes, including apoptosis, excess ROS production, and inflammation.

Telomere shortening and development of CVDs

Progressive telomere shortening, particularly in endothelial cells, was observed in atherosclerotic plaques and areas exposed to disturbed flow. The association between CVD and shortened telomeres has been extensively reported.[12] We and others have reported that disturbed flow increases endothelial cell apoptosis via mitochondrial dysfunction and ROS production.[13] Furthermore, induction of p53 and the TGFβ family by disturbed flow, as well as the contribution of these molecules to endothelial cell apoptosis and dysfunction, have been reported.[14] The crucial role of telomere shortening in endothelial cell biology has been suggested. For example, telomere dysfunction and the resulting senescence of endothelial cells increases synthesis of intracellular adhesion molecule-1, expression of plasminogen activator inhibitor-1, and production of ROS. Van der Loo *et al*. reported that advanced glycation end products promote endothelial cell senescence by increasing mitochondria-derived ROS and concomitant peroxynitrite production, with reduction of nitric oxide

bioavailability and impaired vascular reactivity.[15] Senescence can increase apoptosis of endothelial cells as well as their sensitivity to TNFα and oxidized LDL-induced apoptosis. Reduced nitric oxide bioavailability with increased peroxynitrite production also contributes to senescence-mediated apoptosis of endothelial cells. A number of risk factors for CVD—including smoking, obesity, and diabetes—are known to accelerate telomere shortening. Therefore, the fundamental role and regulatory mechanism of telomere dysfunction in inducing aging phenotypes also applies to endothelial cell pathology.

Telomeres are bound quantitatively by a six-protein complex called shelterin (TRF1, TRF2, TERF2IP, POT1, TPP1, and TIN2 for the mammalian telomere). This complex is essential for telomere length control and stability *in vivo*. Telomere dysfunction is caused mainly by the following three factors: attenuation of telomerase activity, decreased protective effect of the shelterin complex on telomeres, and direct ROS-induced oxidative modification of telomere DNA. Since telomerase activity is already very low in adult tissue,[16] telomere dysfunction induced by telomerase attenuation is rare in adult tissue. There is a tight connection between reduced shelterin effect and direct oxidative modification on the protective effect of telomeres on genomic DNA. The G-rich sequence of telomeres form quadruplex structures in which oxidized equivalents can be trapped. This characteristic of telomeres protects genomic DNA from oxidative damage. Of the four native nucleotides, 2′-deoxyguanosine is the most easily oxidized and forms 8-hydroxy-2′-deoxyguanosine (8-OHdG or 8-oxodG). Although telomeres protect genomic DNA from oxidative damage by sacrificing their own G-rich regions, oxidative damage by 8-OHdG induces telomere dysfunction and subsequently increases genomic DNA damage and apoptosis. Therefore, loss of protection by the shelterin complex accelerates oxidative damage of both telomeres and genomic DNA, which then increases γ-H2AX and its C-terminus phosphorylation and subsequent senescence and apoptosis. Increased levels of 8-OHdG have been reported in atherosclerotic plaques, but the mechanism of 8-OHdG induction by pro-atherogenic stimuli is not known.

Onco-cardiology and the role of premature aging in CVD

Although cancer therapy causes both DNA damage and telomere shortening, only the phenotype of telomere shortening can be transmitted to daughter cells. Therefore, we expect that the late cardiovascular effects of cancer therapy can be explained by this telomere shortening and subsequent premature aging. In other words, by determining the role and regulatory mechanism of telomere shortening and consequent premature aging in cancer survivors, we can obtain crucial information on vascular aging induced by various pro-atherogenic stimuli observed in people without cancer. We believe that future onco-cardiology research will provide crucial information about not only the mechanisms of each cancer drug's side effects but also the key role of premature aging in CVD. Clearly, the future of onco-cardiology should not be limited to cardiologists working in cancer centers, but also include oncologists, cardiologists, and all others who will care for the increasing numbers of cancer survivors with CVD. It is critical that the core knowledge presented in this short essay is shared by all researchers and practitioners.

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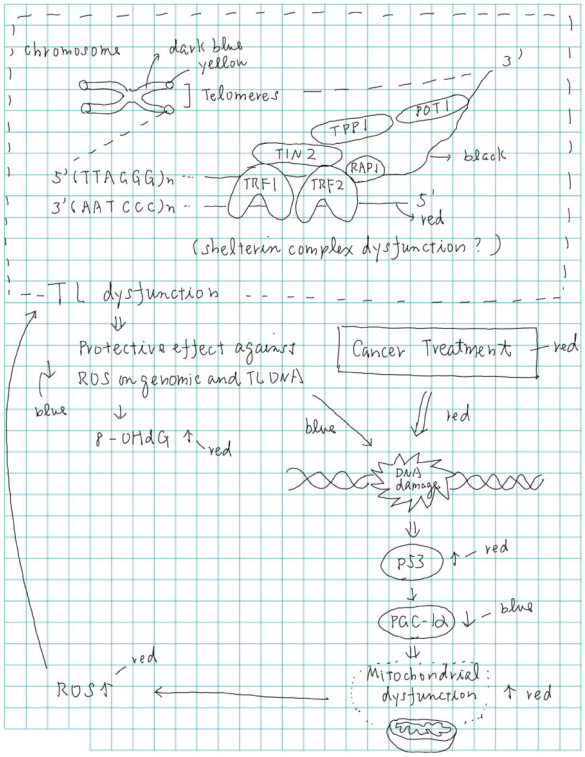

Figure.

Cancer treatment and telomere (TL) dysfunction-related signaling pathways. In this model, DNA damage induced by cancer treatments activates p53 and impairs mitochondrial function via inhibiting PGC-1α expression, which consequently increases reactive oxygen species (ROS) production. This p53-mediated ROS production may reduce protective effects of the shelterin complex, leading to TL dysfunction and additional DNA damage, which forms a positive feedback loop. The acceleration of premature aging induced by TL dysfunction could contribute to cardiovascular diseases (or events) in cancer survivors. PGC-1; PPARγ co-activator 1, 8-OHdG; 8-hydroxy-2'-deoxyguanosine, γ-H2AX; H2A histone family member X and its C-terminus phosphorylation