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Cancer chemotherapy induces cardiotoxicity by targeting cardiac stem cells

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Abstract

Overwhelming data indicate that cancer survivors are at higher risk of cardiovascular diseases because chemotherapy induces cardiotoxicity. Mechanistic explanation of this phenomenon is necessary to advise the clinical practice on the prevention of cardiotoxicity in cancer patients. Here we propose that chemotherapy induces cardiotoxicity by inadvertently interrupting the homeostasis of cardiac stem cells and depleting the resident cardiac stem cells pool. As a result, the heart loses the capability of regeneration and repair and demonstrates the cardiotoxicity symptoms. Our hypothesis is supported by several lines of emerging evidence: the high incidence of cardiotoxicity in paediatric cancer patients who still have more cardiac stem cells in the myocardium; the rescue of anthracycline cardiomyopathy by injection of cardiac stem cells; and the adverse cardiotoxicity induced by inhibitors of oncogenic kinases or pathways which target cardiac stem cells besides cancer cells. This may promote our growing appreciation that cardiac stem cells represent new targets of chemotherapy that contribute to cardiotoxicity and open up novel strategies for the preservation or expansion of the cardiac stem cells pool to overcome cardiotoxicity associated with chemotherapy.

Keywords: cardiotoxicity • cardiac stem cells • chemotherapy • hypothesis

Introduction

Cardiovascular disease and cancer, the two leading causes of death in the industrialized world, are closely linked. Overwhelming evidence has indicated that cancer survivors are at higher risk of cardiovascular diseases because chemotherapy tends to be toxic to the cardiovascular system. For example, breast cancer patients who receive anthracycline therapy are more likely to develop heart failure [1]. Furthermore, a large-scale and long-term study involving 992 men treated for testicular cancer demonstrated that over a 10-year period, nearly 3.5% of those who had undergone chemotherapy developed cardiovascular disease, in contrast to 1.5% of men who had undergone treatment by orchiectomy [2]. This study is striking to reveal the link between cardiovascular disease and cancer chemotherapy in that testicular cancer patients are usually treated with low dose of chemotherapy compared with other types of aggressive cancer. The cardiotoxic risk associated with cancer chemotherapy became more evident recently with the advent of combination therapy and adjuvant therapy. Taken together, mechanistic explanation of this phenomenon is necessary to advise the clinical practice on the prevention of cardiotoxicity in cancer patients undergoing chemotherapy.

Cardiotoxicity

Cardiotoxicity is defined as 'Toxicity that affects the heart' according to the online Dictionary of Cancer Terms in National Cancer Institute (http://www.cancer.gov/dictionary/?CdrID=44004). Cardiotoxicity can be caused by chemotherapy treatment, complications from anorexia nervosa or incorrectly administered drugs. There are two common types of chemotherapy-induced cardiotoxicity: the infrequent form of acute or subacute cardiotoxicity, which occurs anytime from the initiation of chemotherapy up to 2

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weeks after termination of treatment; and the most frequent form of chronic cardiotoxicity. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction that leads to severe congestive cardiomyopathy and may ultimately lead to death. The drugs most commonly associated with cardiotoxicity are anthracyclines, taxanes and alkylating agents. Although the mechanisms underlying acute heart failure and cardiotoxicity remain largely elusive, recent progress in basic and clinical research has led to some theories to explain the molecular details of cardiotoxicity but none of them are completely proved or accepted [3].

Cardiac stem cells

For quite a long time, the heart has been considered as a terminally differentiated organ with no potential of regeneration or repair. Nevertheless, emerging evidence suggests that adult heart like many other tissues also retains a limited population of 'immature' cells. The presence of these stem and/or progenitor-like cells called cardiac stem cells inside the adult myocardial niches challenges the dogma that the heart is a post-mitotic organ. These resident cardiac stem cells express the cell-surface marker, c-kit and possess the fundamental properties of stem cells in that they are self-renewing, clonogenic and multipotent to differentiate predominantly into cardiomyocytes and, to a lesser extent, into smooth muscle cells and endothelial cells in human [4]. Furthermore, this subset of cells has been shown to migrate to damaged regions of the heart and generate new cardiac myocytes in rats, hence reversing the heart failure phenotype and prolonging lifespan [5].

Hypothesis

Our hypothesis is that cancer chemotherapy induces cardiotoxicity by targeting cardiac stem cells. Under normal conditions, the resident cardiac stem cells pool promotes cardiac repair in the heart subjected to various kinds of insult. Nevertheless, in cancer patients undergoing chemotherapy, the anti-tumour agents inadvertently interrupt the homeostasis of cardiac stem cells and deplete the resident cardiac stem cells pool. As a result, the heart loses the capability of regeneration and repair and demonstrates the symptoms of cardiotoxicity.

Evidence supporting the hypothesis

A recent study established the age of cardiomyocytes in humans by taking advantage of the integration into DNA of carbon-14 generated by nuclear bomb tests during the Cold War, and found that cardiomyocytes renew with a gradual decrease from 1% turnover annually at the age of 25–0.45% at the age of 75 [6]. This suggest that the younger population having more cardiac stem cells in the myocardium would be more susceptible to chemotherapy-induced disruption of cardiac stem cells if the above hypothesis is true. This is indeed the case as documented by the high incidence of cardiotoxicity in paediatric cancer patients.

A more direct piece of evidence to support the above hypothesis came from a new study in which the authors employed anthracycline, the most effective drugs available in the treatment of neoplastic diseases [7]. This study demonstrated that anthracycline-induced cardiotoxicity is mediated by the depletion of the cardiac stem cell pool and anthracycline cardiomyopathy is rescued by injection of cardiac stem cells to restore normal cardiac stem cell function.

Protein kinases and cancer have been intimately linked since the first oncogene, src, was identified by Drs. Harold Varmus and Michael Bishop in 1975, and later found to encode a tyrosine kinase. More than 500 protein kinases have been identified up to date, and genes encoding protein kinases are the most commonly mutated in human cancer [8]. Therefore, protein kinases have proved to be promising targets for anticancer therapies. For example, current chemicals for cancer therapy such as imatinib and perifosine target c-Kit and Akt kinase, respectively. Unfortunately, these kinase inhibitors have cardiotoxicity ranging from asymptomatic mild left ventricular dysfunction to congestive heart failure through different mechanisms [9]. Importantly, recent research has revealed that c-Kit and Akt kinases are vitally involved in cardiac stem cell survival, proliferation, differentiation and expansion [10]. Therefore, it is possible that these kinase inhibitors target cardiac stem cells besides cancer cells and induce adverse cardiotoxicity.

Last but not least, it is now well established that many signaling pathways that are classically associated with cancer such as Wnt, Notch and hedgehog also play critical roles in normal stem cell development by regulating the self-renewal and homeostasis of stem cells [11]. This is no exception to cardiac stem cells. For example, Wnt signaling is important for the self-renewal of cardiovascular progenitor cell [12]. Chemotherapy targeting the Wnt pathway in cancer patients may disrupt the cardiac stem cell self-renewal and lead to cardiotoxicity.

Concluding remarks

Although it is still under debate whether cardiac stem cells particularly with cardiomyocyte potential exist in the adult heart and the most convincing evidence so far for cardiac stem cells is during heart development, emerging evidence accumulated so far has led to our conviction that cardiac stem cells become new targets of chemotherapy that contribute to cardiotoxicity in cancer patients. This opens up previously unknown strategies for overcoming cardiotoxicity associated with chemotherapy.

The therapeutic potential of exploiting cardiac stem cells to diminish chemotherapy-induced cardiotoxicity is enormous. For example, when we design and screen new generation of cancer drugs it is absolutely crucial to examine their toxicity to cardiac stem cells as a prediction of their cardiotoxicity before exhaustive clinical trails begin. On the other hand, we can develop up-to-date approaches to promote the preservation or expansion of cardiac stem cells pool to antagonize the depletion of this pool by known cardiotoxic cancer drugs. In certain circumstances, for instance, for cancer patients who could survive only a few months longer, cardiotoxicity may be not a real concern and the efforts to modulate their cardiac stem cells pools may be unnecessary. Whatsoever, there is no doubt that our better understanding of cardiac stem cells biology in the context of cardiotoxicity will provide novel insight into the development of next generation of drugs that effectively eradicate cancer while demonstrate diminished cardiotoxicity.

Conflict of interest

The authors declare that they have no competing financial interests.

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