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Evaluating the Effect of Cancer Stem Cell on Cardio-toxicity: Molecular Mechanism and Future Approach

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Abstract

Background: A rise in the cancer rate causes an increase in the occurrence of cardio-toxic complications while using chemotherapy drugs. Cancer stem cells (CSCs) are cell masses resistant to cancer treatment which escape from cell death by changing signaling pathways. Therefore, increasing the dosage of chemotherapy drugs increases the damage to the heart tissue and the consequences of cardio-toxicity.

Investigating the signaling pathways responsible for the survival of CSCs through changing the amount of reactive oxygen species (ROS), inflammation, and apoptosis, and the effect of these factors on cardiomyocytes at the molecular level can provide a more detailed view of how the cardiotoxicity process works. Among the important signaling pathways involved in the cardiotoxicity process, through the three processes of increasing oxidative stress, inflammation, and apoptosis, we can mention Notch, pI3K/AKT, wnt signaling pathways, and NF-kB. This approach can suggest therapeutic methods capable of destroying CSCs with less cardiotoxicity effects.

Conclusion: Finally, as a hypothesis, it can be said that effective factors on the survival of CSCs can influence the cardio-toxicity by impacting ROS, inflammation, and apoptosis process.

Keywords: Cancer stem cell, Cardiotoxicity, Molecular mechanism, Pathogenesis

1. Background

During the economic and social development, age increment, population growth, and lifestyle changes, the global rate of cancer increases, followed by an increase in mortality. According to predictions, 28.4 million people will be diagnosed with cancer by 2040, which represents 40% increase in cases compared to 2020 (with 19.3 million cases)(1).

Cancer is a heterogeneous disease caused by successive mutations in the genes, regulating the cell cycle and oncogene (2, 3). Chemotherapy, as a well-known method for cancer treatment, destroys cancer cells by processes such as apoptosis, directly affects DNA, and disrupts the function of key proteins for cell division; it also affects bone marrow and mucous membranes (4, 5). In addition, chemotherapy agents can cause cardio-toxic effects, such as left ventricular dysfunction and heart failure (6-8)(Table 1).

Despite the extensive achievements in the field of cancer treatment, the resistance of tumor cells to the treatment methods is still a major challenge. One of the principal indicators used during the cancer treatment process to evaluate the success of a treatment method, is the minimal residual disease (MRD). At least, cancer cells that remain in the body during and after treatment are called MRD (9). Examining the MRD index shows that there are many cancer cells with the characteristic of self-renewal in MRD (10). These cells are called cancer stem cells (CSCs) and are among the factors that cause cancer treatment methods to fail. These cells are a type of tumor-forming cells with the same self-renewal properties as normal body stem cells, with the difference that this property has not been regulated in CSC (11, 12).

Due to the resistance of CSCs to chemotherapy, higher doses of chemotherapy drugs are used to control the disease, ultimately leads to the occurrence of cardiotoxicity complications at a higher rate. For instance, trastuzumab inhibits the autophagy process, and increases the amount of reactive oxygen species (ROS), and ultimately cardiotoxicity by disrupting the HER2 signaling pathway and activating Erk and increasing mTOR signaling (13). Doxorubicin, as one of the most common chemotherapy drugs, leads to cardiotoxicity through various mechanisms, including increasing the expression of death receptors (TNFR1, Fas, DR4, and DR5), which leads to apoptosis in cardiomyocytes (14, 15). Many studies have been conducted on the impact of chemotherapeutic drugs

on the pathogenesis of cardiotoxicity. However, the effect of CSCs has not been the examined. Based on the fact that CSCs are resistant to apoptosis and are not sensitive to chemotherapeutic drugs, they can potentially contribute to the cardiotoxicity development.

Many studies have been conducted in relation to chemotherapy and cardio-toxic effects; however, a limited number of studies has been conducted on the effect of CSCs on cardiotoxicity. Therefore, the present study examined the molecular mechanisms related to the effect of CSCs in the occurrence of cardiotoxicity.

Table 1. Summary of some drugs causing cardiotoxicity

Drugs	Mechanism	Potential cardiotoxicity	Ref
Doxorubicin	Notch/HES1/PARP1/AIF involved in apoptosis	NADPH oxidase/ ROS-mediated NF-kB signaling cascade involved in apoptosis.	(16) (17)
Trastuzumab	MAPK and PI3K/Akt involved in cell cycle arrest.	Autophagy- inhibitory Erk/mTOR/ULK 1 signaling cascade involved in ROS generation.	(18) (19)
Cyclophosphamide	Type 1 INF and p53 involved in inflammation.	P38/MuRf1/MLCK involved in cardiac apoptosis. NF-kB p65/TNF-α/IL-6, IL-1β, involved in cardiac inflammation.	(20) (21)
Sunitinib	Nrf2/GSTA1 involved in oxidative stress.	ETC complexes inhibition/ROS/SOD2/caspase3 involved in apoptosis.	(22) (23)
Docetaxel	P53/Bcl-2/thioredoxin involved in apoptosis.	ATF6/CHOP/Bip involved in apoptosis.	(24) (25)

1.1. Cancer stem cell and oxidative stress

The use of high doses of chemotherapy drugs to destroy CSCs increases the amount of produced ROS and changes the regulation of signaling pathways in cardio-myocytes and cardio-toxicity. The comparison of these signaling pathways in CSC and cardio myocytes can lead to the identification of drug compounds that can reduce cardiotoxicity when used simultaneously with chemotherapy.

One of the pathways that affect the amount of ROS in CSCs is the Notch signaling pathway, which affects stemness and cell differentiation. Inactivation of the Notch pathway decreases aldehyde dehydrogenase positive cells that have self-renewal characteristics (26). Inducible nitric oxide synthase (iNOS), as the main system producing ROS by activating TACE/ADAM17 activates the Notch1 pathway and causes the preservation of stemness in CSCs (27). Notch1, by affecting PI3K/AKT and increasing the expression of AKT, leads to an increase in the expression of ROS scavenging enzyme, which leads to ROS reduction in CSCs and maintaining hypoxia conditions (27).

In fact, AKT activity increment is associated with increased expression of mTOR, which can lead to the activation of HIF-1α through the phosphorylation of eukaryotic translation initiation factor 4E-binding protein (4E-BP1) and p70S6 kinases (S6k)(28). Transcriptional targets of HIF-1α include VEGF and FOXOs, which are associated with stemness properties and ROS scavenging (Figure 1) (27). In hypoxic conditions, HIF-1α through interaction with NICD, leads to preservation of stemness in glioma stem cells (28). The HIF-1α factor initiates the cardio protection process by increasing the expression of erythropoietin, iNOS, hemeoxygenase-1 (HO-1), and SDF-1; therefore, in the conditions of oxidative stress and increased ROS levels, the stability of HIF-1α reduced, which ultimately increases cardiotoxicity (29, 30). Both HIF-1α and HIF-2α are involved in the activation process of Notch pathway, and Notch activation leads to the expression of the epidermal growth factor receptor type 2 (HER2), which preserves the stemness characteristic and balances the ROS level in breast CSCs (27).

At the same time, inhibition of Notch1 pathway under the influence of oxidative stress leads to apoptosis in cardiomyocytes (31). Additionally, increasing the expression of microRNA-208a can increase the amount of malondialdehyde and inhibits SOD, GSH, GSH-px, and also increases ROS and induces the p65 expression .

In addition, in this study, it has been shown that the activation of the Notch1 pathway reduces the effect of microRNA -208a and inhibits the induction of p65 and prevents cardiotoxicity (32). The PI3K/AKT/mTOR signaling pathway, which affects survival and cell cycle regulation is one of the signaling pathways that has a two-way relationship with ROS levels in CSCs. An increase in ROS levels in CSCs activates the PTEN/PI3K/AKT signaling pathway; by affecting the expression of FOXOs genes, with the activation of forkhead transcription factor FOXO3a, it activates the production of manganese superoxide dismutase (MnSOD) as a type of ROS-scavenging enzyme, and ultimately decreases cellular ROS levels (Figure 1) (33, 34).

The PTEN is one of the upstream factors and negative regulator of this pathway; under the influence of high ROS, one of the cysteine residues in the catalytic site Of PTEN oxidized and caused its inactivation and also the activation of the PI3K/AKT pathway, which eventually leads to the regulation of ROS level (Figure 1) (35). Oxidative stress in heart cells can lead to cardiotoxicity by affecting the PTEN/PI3K/AKT pathway. Oxidative conditions in H9c2 cells lead to an increase in CYP1A1 enzyme activity as well as an increase in

the production of reactive metabolites. In such conditions, an increase in the expression of FOXO3a leads to an increase in the expression of PTEN; finally, it leads to the initiation of apoptosis and heart damage. On the other hand, in this study (36), it has been shown that the change of CYP1A1 enzyme activity, as one of the types of cytochrome p450 (CYP), which is involved in the conversion of

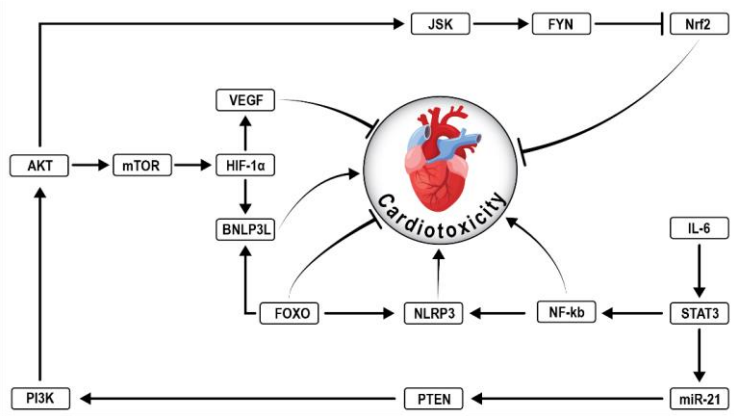

Figure 1. The molecular pathway involved in the development of cardiotoxicity through CCSCs is mediated by IL-6. The IL-6 activates inflammation through STAT3 and NF-kB. On the other hand, AKT is one of the targets of IL-6 that becomes activated. The HIF-1α is also activated by AKT. Its activation leads to the occurrence of cardiotoxicity

arachidonic acid to epoxyeicosatrienoic acids and hydroxyeicosatetraenoic acid can interfere in the occurrence of cardiotoxicity.

Decrease in GSH/GSSG ratio and increase in HEL as a marker of free radical induces lipid peroxidation signaling in the left ventricle, as well as increase in AKT expression in heart cells that have suffered cardiotoxicity; it indicates that increase in myocardial AKT expression in oxidative conditions improves heart failure. The result of these conditions is effective (37). However, it has been shown that long-term oxidative stress causes decrease in the phosphorylation and activity of AKT and also facilitates the conditions for cardiotoxicity (38). In addition, AKT can also affect ROS in cardiomyocytes through another pathway. In this pathway, AKT dephosphorylation leads to GSK3β/FYN activation and FYN nuclear accumulation, which causes Nrf2 to leave the nucleus and degrade it in the cytoplasm.

In this way, reducing Nrf2 causes reduction in the expression of antioxidant proteins, including HO-1 (39). On the other hand, decreasing the expression of mTOR and MnSOD in cardiomyocytes increases cardiotoxicity by increasing the ROS level (40-43). Therefore, it can be assumed that, increasing the expression of mTOR and MnSOD by affecting ROS in CSCs, and then changing the regulation of mTOR and MnSOD in cardio-myocytes can increase cardiotoxicity. The Wnt signaling pathway is another crucial pathway in CSCs; targeting the Wnt signaling pathway increases the sensitivity to ROS. The high level of ROS inhibits the expression of β-catenin.

In the oxidative stress conditions applied through H2O2, the interaction between Nucleoredoxin and Dishevelled (Dvl) is inhibited, and the Wnt/β-catenin pathway is blocked. Also, in another study, it has been shown that increased expression of FBP1 in basal-like breast CSCs decreases β-catenin pathway signaling by increasing the process of oxidative phosphorylation and the ROS production (44).

Fructose 1, 6-bisphosphatase (FBP) effectively regulates glucose and glycogen synthesis, protects cardiac mitochondria against the stress of high calcium concentration, and is also involved in regulating the cell cycle of cardiomyocytes. Evidence on how FBP can affect cardiotoxicity is not available. Glutaminase 1 (GLS1) is a mitochondrial matrix protein which has caused the preservation of stemness and increased the expression of CSC markers in liver CSCs by regulating the ROS level and affecting the Wnt/β-catenin signaling pathway. Inhibition of GLS1 has reduced stemness in HCC and lung CSCs (44). Inhibition of GLS1 reduces the conversion of Glutamine to Glutamate; in this way, the amount of GSH as one of the antioxidant factors decreases, which leads to an increase in the ROS level followed by a decrease in the expression of β-catenin. It causes a decrease in the expression of target genes of the β-catenin pathway.

Most genes whose transcription is activated by the Wnt pathway are CSC markers (44). Unlike CSCs, in rat neonatal cardiomyocytes under oxidative conditions, the activity of GLS increases, and through the reduction of ATP production and GSH synthesis, it reduces the survival of heart cells (45). On the other hand, the Wnt signaling pathway can also activate the PI3K/AKT pathway, which makes CSCs resistant to ROS (27). Unlike CSCs, which have ROS-modulating mechanisms, cardiomyocytes are sensitive to oxidative stress; for example increasing the expression of lincRNA-p21 decreases SOD and increases the amount of ROS, and decreases the

expression of the Wnt/β-catenin pathway; finally, it will lead to cardiotoxicity increment (46, 47).

In another study, increase in ROS level caused an increase in DKK1, which causes disturbances in the normal function of cardiomyocytes with its antagonistic activity on the Wnt/β-catenin pathway (48). Also, an increase in ROS in cardiomyocytes can lead to decrease in GSH activity and increase in cardiotoxicity (49). Therefore, regulating the Wnt/β-catenin signaling pathway in CSCs and changing GSH expression by affecting oxidative stress and reducing the GSH activity in cardio-myocytes leads to an increase in the incidence of cardiotoxicity. According to the mentioned materials and the signaling mechanisms and pathways, it can be concluded that an increase in the expression of Notch, PI3K/AKT, and Wnt/β-catenin signaling pathways in CSCs leads to the adjustment of ROS levels; while in cardio myocyte, the inhibition of these pathways leads to cardiotoxicity caused by ROS. Therefore, to reduce the cardio-toxic effects during the use of chemotherapy drugs, it is necessary to use drug treatments that regulate these pathways at the same time.

1.2. Cancer stem cell and Inflammation

In recent years, the effect of inflammation on the development and progression of cancer has been noticed. Additionally, using inflammation control drugs for the treatment and control of cancer has been considered a new strategy (50). Inflammatory cytokines, such as TNF-α, IL-1B, IL-6, and TGF-β, are released from tumor cells and the surrounding environment during chronic inflammation, and play a major role in cancer progression (51). The amount of inflammatory cytokines in CSCs is higher than normal cells; on the other hand, the high level of inflammation in these cells causes molecular mechanisms of resistance to chemotherapy to be launched; and the use of high doses of chemotherapy substances causes cardiotoxicity. Therefore, identifying the inflammatory pathways that lead to cardiotoxicity will be helpful in identifying treatment methods which reduce the side effects of chemotherapy.

The IL-1 is one of the inflammatory factors in breast CSCs. It has higher expression compared to the differentiated tumor parts; it activates the IKK, which leads to phosphorylation of Ikβ and removing the inhibitory effect of this factor on NF-kB, and also by transferring NF- kB to the nucleus transcription of the inflammatory mediators, including IL-6 is activated (52-55). On the other hand, the secretion of IL-6 by inflammatory cells causes the activation of STAT3 in CSCs, and leads to the activation of miR-21 and miR-181b-1, which inhibit PTEN and CYLD, respectively. Also, many other miRs are involved in cardiotoxicity (Table 2). By inhibiting CYLD, the activity of NF-kB increased, which leads to an increase in the production of IL-6 and IL-8, and a positive feedback loop is created, which causes the maintenance of chronic inflammation in CSCs (52, 56, 57).

Table 2. Evaluation of mechanism of miRs on cardiotoxicity

MicroRNA	Mechanism	Ref.
miR-34a-5p	miR-34a-5p/Sirt1/p66shc involved in mitochondrial apoptosis pathway.	(89)
miR-526b-3p	miR-526b-3p/STAT3/VEGFA involved in vascular injury.	(90)
miR-199	miR-199/TAF9b involved in cardiomyocytes apoptosis.	(91)
miR-140-5p	miR-140-5p/Nrf2, miR-140-5p/Sirt2 involved in myocardial oxidative damage.	(92)
miR-494-3p	miR-494-3p inhibits MDM4 and activates p53 and promotes cardiomyocytes apoptosis.	(93)
miR-146a	Down regulated miR-146a/PLN,ANK2 involved in cardiac contractile dysfunction.	(94)
miR-125b	miR-125b/STARD13/YAP axis involved in cardiotoxicity.	(95)

Previous studies related to the effect of IL-6 on cardiomyocytes showed that the expression of IL-6 factor in a sufficient amount causes the survival of heart cells against acute inflammatory conditions; however, overexpression of IL-6 in chronic inflammation damages the heart tissue. The IL-6 activates the JAK/STAT signaling pathway through glycoprotein-130 (gp130). During acute inflammation, the activation of the JAK/STAT pathway through the phosphorylation of STAT3 leads to the inactivation of caspase-3, and the initiation of the anti-apoptosis pathway, thereby causing the survival of cardiomyocytes. However, decreased expression of the protein suppressor of cytokine signaling, which is a negative regulator of the gp130/JAK/STAT pathway will result in continuous IL-6 signaling; it induces a continuous anti-apoptotic program, which leads to lose the efficiency of heart muscle and heart failure (58, 59).

In another study, excessive increase of IL-6 by affecting TNF-α caused damage to heart tissue (60). In fact, IL-6 affects cardiomyocytes in a different way, based on the duration and amount of its signaling (58). With the activation of NF-kB in the positive feedback loop created by IL-6, two factors, lin-28 and let 7, also cause the CSCs survival (52). In another study, reducing the induction of lin28B and Let 7, as well as reducing the production of inflammatory molecules such as IL-1α, IL-1β, IL-6, and VEGF through the reduction of the production of the phosphorylated form of STAT3 caused the inhibition of NF-kB activity, which ultimately reduced the amount of CSCs (61).

However, in a study, it was shown that the

inactivation of Lin28a, which plays the central role in creating the hypertrophy process in mouse heart cells, has caused the proper functioning of the heart to be preserved (62). In fact, lin-28a diverts the carbon flux from the TCA cycle to glycolysis by directly binding to the phosphoenolpyruvate carboxy kinase mRNA gene; it increases the stability and expression of this gene, and causes an increase in the flux of anabolic pathways from glycolytic intermediates for supporting cell proliferation and growth, which is required to initiate the pathological hypertrophy process of the heart (63).

Another inflammatory factor that maintains chronic inflammation in CSCs is IL-8, which facilitates the angiogenesis process by stimulating VEGFR2, and thus causes the survival of CSCs (51). Increase in IL-8 following the activation of the NF-kB signaling pathway in cardio-myocytes also increases TNF-α (64). The TNF-α also activates Caspase-8 through its receptors called TNFR1 and TNFR2, and following activity increment, a molecule called BID is activated. The BID transfer from the cytosol to the mitochondria and the release of cytochrome C into cytosol causes cardiotoxicity (65).

Therefore, although the increase of IL-8 with the increase of inflammation causes the preservation and survival of CSCs, it has a destructive effect on the heart tissue. Also, examination of damaged heart cells has shown that in addition to pro-inflammatory factors such as TNF-α and IL-6, iNOS is also high in cited cells. The iNOS is an inflammatory mediator whose expression increases under the influence of inflammatory cytokines, and increases the production of NO as a signaling molecule, which is involved in physiological and pathological processes (66, 67). The increase in NO production under the influence of increased expression of iNOS in cardio-myocytes can lead to consequences such as inhibiting L-type Ca2+ channel, inhibiting the mitochondrial respiratory chain, and increasing the permeability of the mitochondrial membrane, all of which lead to apoptosis (68).

In fact, NO inhibits the activity of this calcium channel by influencing the activity of Guanylate cyclase and the cGMP level (69). High concentration of NO produces Proxynitrite as a result of reaction with oxygen, which damages respiratory chain complexes through oxidizing reactions and causes irreversible inhibition of their activity (70). Also, the continuous production of NO will result in the continuous inhibition of complex 1 of the respiratory chain (70). Furthermore, the increase in NO concentration causes an increase in the expression of BAX compared to Bcl-2, which leads to apoptosis. Apoptosis process is carried out by NO through TNF-α factor (70).

In damaged heart cells, the level of IL-10 as an anti-inflammatory factor was lower than normal cells (71). In this research (72), it has been shown that the increase of IL-10 by increasing the phosphorylated form of AMPKα and SIRT1 through post-translational regulation causes an increase in the activity of FOXO3a and thus exerts its cardio protective effect. All the mentioned cases indicate the effect of inflammation on the induction of cardiomyopathy. In another study, heart tissue damage markers such as LDH and CK-MB are higher in cells that have a high level of TNF-α, IL-1B, IL- 6, and NF-kB.

In addition, there is a higher level of p-FOXO3a in the cells that did not suffer from cardiac complications, indicating the cardio protective role of this factor (73). The Foxo3a is involved in various processes, such as autophagy, apoptosis, and cell cycle arrest. It also regulates inflammatory processes through the regulation of NF-κB. However, the phosphorylated form of FOXO, which is phosphorylated under the influence of AKT, causes FOXO to leave the nucleus, which inhibits apoptotic processes (74). Also, in another study, it has been shown that increasing the entry of FOXO3a from the cytoplasm into the nucleus causes the activation of the transcription of its downstream genes; one of these downstream genes is BNLP3L; its protein disrupts cell respiration, which is involved in the process of cell necrosis and cardiotoxicity (75).

The IL-1B factor leads to cardiotoxicity by increasing the amount of Ca in cardiac cells (76). However, detailed evidence of the molecular mechanism of this process is not available. Furthermore, in damaged heart cells, NLRP3 inflammatory complex is created, and through CAS-1 causes the production of IL-1B and IL-18. The NF-κB affect NLRP3 regulation, and inhibiting NF-κB and NLRP3 reduces the production of inflammatory cytokines and cardiotoxicity (77). According to the report of this study (78), knock down mutation in FOXO3a gene increases the expression of pyroptotic and inflammatory genes, including NLRP3, caspase-1, IL-1B, and IL-18 in cardio-myocytes. According to the studies, NLRP3 expression is increased in SCCHN and gastric cancer CSCs (79, 80). It seems that increased expression of NLRP3 causes cancer progression through increased expression of IL-1β (79). However, the molecular mechanism by which CSCs increase NLRP3 expression is unclear. In this way, another factor that CSCs can use to affect the cardiotoxicity process is NLRP3, which is important as one of the therapeutic goals to reduce heart complications.

The EGFR factor is another factor that has increased the expression in various types of CSCs, and has an effect on inflammation. In a study, it has been shown that CSCs increase inflammation through the EGFR/COX-2/Nodal pathway. In fact, the EGFR pathway, by regulating the expression of COX-2, which is an important molecule in creating an inflammatory response, increases the production of prostaglandins such as PGE2 and PGF2α; also, COX-2 increases the inflammation in CSCs by increasing the

expression of Nodal and activating this signaling pathway (81). Unlike CSCs, which inflammatory factors increment has a strengthening effect on them, the inflammation enhancement in heart cells will result in heart tissue damage and cardiotoxicity.

A decrease in COX-2, iNOS, and Caspase-3 in cardio-myocytes, which indicates a reduction in inflammation, will lead to reduction in cardiotoxicity and heart tissue damage markers, such as LDH and CK-MB (82). In another study, oxidative stress causes the activation of NF-kB, followed by activation of inflammatory response and increased production of TNF-α and COX-2, leading to an increase in cardio-toxicity through apoptosis (83). Therefore, it can be assumed that CSCs can lead to cardiotoxicity through the COX-2 increase and due to the inflammation increment.

In addition to the above pathway, EGFR causes heart damage through the activation of ERK1/2, PI3K/AKT, NF-kB, and smad2/3/4 signaling pathways through the growth of cardiomyocytes, inflammation, cardiac fibrosis, and finally, cardiac hypertrophy (84). However, recent studies have shown that increased expression of ERK1/2-Nanog, PI3K/AKT, NF-kB, and Smad2 signaling pathways (as one of the most important types of Smad) increases the amount of CSCs (85-88). Therefore, it can be assumed that CSCs can create the conditions for cardiotoxicity by increasing the expression of the mentioned signaling pathways and by increasing the expression of the EGFR2 pathway.

Therefore, according to the mentioned materials, the increase in inflammation and the production of inflammatory factors is another mechanism by which CSCs maintain their survival against chemotherapy. The high level of inflammatory factors is harmful to heart cells and leads to cardiotoxicity; as a result, to reduce the cardio-toxic effects, it is necessary to prevent the occurrence of heart damage by influencing the pathways that cause inflammation.

1.3. Cancer stem cell and apoptosis

Another characteristic of CSCs is their resistance to apoptotic mechanisms, which causes their survival against chemotherapy and radiotherapy (96). Therefore, understanding the molecular mechanisms that lead to the escape of apoptosis pathways in CSCs and the effect of these mechanisms in the cardiotoxicity process can suggest methods that can eradicate CSCs and reduce cardio-toxic complications. Cytotoxic drugs and radiation eliminate cancer cells by activating the intrinsic and extrinsic apoptotic mechanisms (97).

However, there are mechanisms in CSCs to escape from apoptosis. Some of these and their effects on cardiomyocytes will be examined in the following. One of the signaling pathways of the extrinsic type is the signaling pathway dependent on the TNF-related apoptosis-including ligand death receptor (DR). It is expressed by monocytes and dendritic cells under the influence of interferon-β, which has anti-tumor properties (98). The TRAIL can bind to different receptors, including DR (e.g., DR4 and DR5), as well as decoy receptor, including DcR1 and DcR2 (98). The difference between the two types of receptors is the absence of the cytoplasmic part, which is necessary to trigger the apoptosis process (98).

After TRAIL binding to the receptor, the apoptotic pathway is activated, and by using the FADD adapter molecule, Caspase 8 and Caspase 10 are activated, and by activating the Caspase 3, Bid is activated and binds to Bcl-XL; it leads to the release of Mitochondrial cytochrome c and second mitochondria of caspase (smac) move into the cytosol. Then, cytochrome C with Apaf-1 activate caspase-9, followed by activation of Caspase 3 and 7, and leads to apoptosis (99). Caspases cause the activation of Caspase-activated DNase (CAD) by making a cut on ICAD/DFF45 and its entry into the nucleus, which eventually fragments the DNA and causes apoptosis (100). Among the mechanisms that disrupt the apoptosis process by TRAIL in CSCs, we can mention the decrease in the expression of DR4 and DR5 and the increase in the expression of DcR1 and DcR2, which are anti-apoptotic receptors (98).

On the other hand, the activation of TRAIL-R4, a type of decoy receptor, leads to the induction of anti-apoptotic genes in CSCs through the NF-kB activation (98). Meanwhile, the increase in TRAIL produced by the immune system to suppress cancer cells along with blood circulation is placed in the vicinity of cardio-myocytes; it leads to the activation of the external pathway of apoptosis and cardiotoxicity through increasing the expression of DRs and inducing the formation of the DISC complex (101). In addition, the expression level of FLICE-like inhibitory protein (FLIP) in CSCs is higher than non-CSCs. In fact, CSCs by increasing the expression of FLIP and inhibiting the binding of Caspase-8 to FADD, prevent the accumulation of the DISC complex and show resistance to TRAIL-mediated apoptosis (98, 99).

It has also been shown that the increase in nuclear cFLIP expression increases the expression of target genes of the Wnt pathway and increases CSCs; however, decrease in Wnt/B-catenin expression is involved in regulating the sensitivity of CSCs to TRAIL and reducing the EMT process (98). This study (102) has investigated the effect of reducing the amount of cFLIP on the amount of CSCs through siRNA; by inhibiting cFLIP, the expression of Wnt and B-catenin signaling pathways decreased, which led to decrease in the number of CSCs. Unlike CSCs, in cardio-myocytes, as a result of overexpression of NF-kB, the expression of cFLIP decreases, which increases the sensitivity of these cells to TRAIL the circulation; this process causes the activation of the external pathway of apoptosis and cardiotoxicity (103). Therefore, one of the factors through which CSCs can affect

cardiotoxicity is the pathway activated by TRAIL; it should be considered in order to reduce the cardio-toxic effects during chemotherapy.

Another proteins involved in regulating the process of apoptosis in CSCs are inhibitor of apoptosis proteins (IAP) that prevent apoptosis by inhibiting endogenous caspases (96). The IAP factors, including Survivin, XIAP, c-IAP1, and Livin, have higher expression in CSCs than non-CSCs (99). The XIAP factor is one of the strongest types of IAPs, which causes resistance to the apoptosis process by binding to Caspase-3 and Caspase-7, and inhibiting the activity of Caspase-9. On the other hand, the connection of XIAP to NF-kB transcription factor can also activate the survival signal in CSCs (96).

However, in a study, it has been shown that increasing the expression of cellular communication network factor 1 (CCN1) in cardio-myocytes by involving integrinβ6β1 through increasing the activity of p38-mitogen-activated protein kinase caused the release of smac and HtrA2 from mitochondria to the cytosol, and counteracted the inhibition process of XIAP, and facilitates the process of apoptosis. Disruption of CCN1/β6β1 interaction prevents cardiomyopathy (104). On the other hand, reducing the expression of CCN1 by affecting the YAP signaling pathway inhibits the mitophagy process (105). Since the process of mitophagy causes the expansion of CSCs, the activation of the CCN1 pathway causes the expansion of CSCs; consequently, it can be assumed that CSCs through the CCN1 factor can lead to the inhibition of XIAP in cardiomyocytes, and the initiation of the process of apoptosis and cardiotoxicity.

Another mechanism related to XIAP that leads to apoptosis in CSCs, is apoptosis related protein in TGF-β signaling pathway (ARTS/septin4 isoform 2), which is involved in apoptosis through direct binding to XIAP; in such a way, the mice that are disturbed in this signaling pathway have more CSCs (106). On the other hand, Septin4 can activate the PARP1 and ultimately intensify the apoptosis process by binding to PARP1 in the conditions of oxidative stress in endothelial cells (107). Also, in another study, it has been shown that the excessive increase of Septin4 causes an increase in the amount of cleaved Caspase-3; moreover, in the condition of hypoxia and through the inhibition of HIF-1α, which is responsible for creating adaptation in the hypoxia, it causes exacerbation. Cardiac cells are damaged through apoptosis (108). Therefore, Septin-4another should be considered to reduce cardio-toxic effects during chemotherapy.

In addition to the mentioned cases, anti-apoptotic proteins of the Bcl-2 protein family, which include Bcl2, Bcl-XL, and MCL-1 proteins, increase the amount of CSCs by inhibiting the signaling of the internal apoptosis pathway (99). The internal pathway of apoptosis occurs via changing the permeability of the mitochondrial outer membrane and the release of apoptogenic factors from the mitochondria to the cytosol, including cytochrome C, apoptosis, inducing factor (AIF), smac/direct IAP binding protein with low PI (DIABlo), and omi/ high temperature requirement protein A2 (HtrA2) (96). The release of cytochrome C into the cytosol activates Caspase-3 through the formation of the Apoptosome complex containing cytochrome c/Apaf-1/caspase-9. Smad/DIABLO enhances the activation of caspases by neutralizing the IAPs (96). Bcl 2 protein inhibits the apoptosis process in CSCs by blocking the permeability of the mitochondrial outer membrane (96).

Inhibition of Bcl2 increases the sensitivity of CSCs to TRAIL treatment and decreases the amount of CSCs (97). In CSCs, the PI3K/AKT signaling pathway is active, and the activation of this pathway leads to increase in the expression of anti-apoptosis factors, including Bcl2, Bcl-XL, and MCL-1, as well as a decrease in the expression of pro-apoptotic factors, including Bid, BAX, and Bim (98); however, inhibition of phlpp1 activity through positive regulation of AKT/Bcl-2 reduces cardiotoxicity through inhibition of apoptosis process (109). The Phlpp1 can also prevent the phosphorylation of Mcl-1 at thr163 position through binding with myeloid anti-apoptosis protein (MCL-1) or dephosphorylation of the phosphorylated form of MCl-1. The phosphorylated form of MCL-1 has a slower turnover rate. Therefore, the lack of PHLPP1 increases the stability of MCL-1 and increases the expression of this anti-apoptotic protein; thereby, it reduces the occurrence of cardiotoxicity (109). In another study, it has been shown that PHLPP1 inhibits AKT activity through dephosphorylation of AKT, thus providing the conditions for apoptosis and tumor suppression (110). Therefore, CSCs can also affect cardio-myocytes through PHLPP1. To identify treatment methods along with chemotherapy to reduce cardio-toxic effects, CSCs can be further investigated.

Therefore, according to the above, it can be concluded that although the resistant mechanisms to apoptosis cause CSCs to escape from the mechanisms of apoptosis, the conditions of oxidative stress and high inflammation cause the initiation of apoptosis processes in cardio-myocytes and increase cardiotoxicity.

2. Conclusion

Extensive studies have been conducted in order to find appropriate treatment solutions to eliminate CSCs that cause cancer survival in patients. However, according to the mechanisms of CSCs against therapeutic agents, the occurrence of cardio-toxic complications in cancer patients is growing statistically.

In fact, the main problem here is that CSCs have

resistant mechanisms to common cancer treatment methods, while cardiac cells lack such mechanisms. Therefore, investigating the molecular mechanisms and resistant signaling pathways in CSCs and their effects on cardiotoxicity can be impressive in providing new and appropriate treatment strategies. The above studies showed that different molecular pathways in CSCs can lead to cardiotoxicity by changing the amount of ROS, inflammatory factors, and factors affecting apoptosis. Therefore, the use of therapeutic methods that control these signaling pathways in CSCs and cardio-myocytes, along with conventional cancer treatment methods, can reduce the occurrence of cardio-toxic complications.

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Footnotes

Conflicts of Interest: None.

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