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Research Progress on the Mechanism of Cardiotoxicity Caused by Doxorubicin and Its Treatment by Traditional Chinese Medicine

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Abstract: Doxorubicin is a widely used antitumor drug, but its cardiotoxicity limits its clinical use. This paper reviews the main mechanisms of Doxorubicin causing cardiotoxicity, including topoisomerase IIβ, oxidative stress, mitochondrial function, calcium homeostasis, autophagy, and apoptosis, etc. It also introduces some novel targets and strategies, such as the CRTH2 receptor, the Nrf2 signaling pathway, the SIRTs family of proteins, and the progress of the research on the treatment of traditional Chinese medicine. This paper aims to provide new ideas and directions for the prevention and treatment of Doxorubicin cardiotoxicity.

Cancer is the second leading cause of death globally and remains a major public health problem in our country. The latest data show that the incidence of malignant tumors in China continues to rise[1].Cancer not only brings great pain to patients, but also imposes a heavy financial burden on families and society. Traditional chemotherapy remains an important cornerstone of cancer treatment. As the number of cancer survivors has increased dramatically over the past three decades, there has been a growing recognition of the importance of the side effects of cancer treatment, among which cardiotoxic reactions caused by chemotherapeutic agents are particularly prominent.

Doxorubicin (DOX) is an anthracycline-based chemotherapeutic agent that has been shown to have therapeutic effects on a wide range of cancers, including acute leukemia malignant lymphoma, breast cancer, bronchopulmonary cancer, ovarian cancer, soft tissue sarcoma, and hepatocellular carcinoma[2,3].DOX has dose-dependent and cumulative cardiotoxicity, which can cause irreversible cardiomyocyte damage, cardiomyocyte apoptosis, necrosis, myocardial dysfunction, dilated cardiomyopathy, and heart failure, and therefore, its clinical application is limited.

Currently, modern medicine has limited efficacy in combating Doxorubicin-induced cardiotoxicity (DIC). Novel targets bring hope for the prevention and treatment of DIC, but the corresponding drugs lack clinical research data and remain controversial. Traditional Chinese medicine (TCM) has unique advantages in the prevention and treatment of DIC, and it can enhance clinical efficacy and improve the quality of life of tumour patients, showing great potential for application. The aim of this paper is to review the mechanism of Doxorubicin-induced

cardiotoxicity and to make a summary of the current mechanism of Chinese medicine in treating DIC, so as to provide new ideas and methods for the prevention and treatment of Doxorubicin.

1. Mechanism of Doxorubicin-induced cardiotoxicity

1.1 TopoisomeraseIIβ

Topoisomerase (TOP) IIβ is present in all cells and is similarly expressed in adult cardiomyocytes. Doxorubicin binds to Top IIβ in cardiomyocytes, forming an unstable enzyme-DNA cleavage complex that leads to DNA double-strand breaks and oxidative damage, which in turn triggers cardiomyocyte apoptosis or necrosis. Dexrazoxane antagonises the formation of TopIIα and TopIIβ cleavage complexes and ameliorates DIC by specific binding to TopIIβ isozymes thus.Similarly a study found that mitochondrial topoisomerase 1 (TOP1mt) knockout mice died within 45 days of the last injection of Doxorubicin, whereas wild-type mice survived, suggesting that Top1mt may be a new limiting factor in DIC[4].

1.2 Oxidative stress

Oxidative stress refers to the dysregulation of the balance between reactive oxygen species (ROS) and reactive nitrogen species (RNS) and antioxidants.DOX can generate ROS and RNS through a variety of pathways, including damage or inhibition of the mitochondrial electron transport chain, NADPH oxidase, and disturbed iron metabolism[5].ROS and RNS can lead to molecular damage such as DNA damage, protein oxidation, and lipid peroxidation, which in turn activate cytotoxic signalling pathways such as MAPK, p53, and NF-Kb[6].

1.3 Mitochondrial function

DOX can damage mitochondria in a variety of ways, by directly binding to cardiolipin in the inner mitochondrial membrane, interacting with phospholipids, altering mitochondrial membrane properties and disrupting the activity of transporter proteins, interfering with mitochondrial DNA and protein synthesis, and inducing the opening of the mitochondrial outer membrane permeability transition pore (mPTP), among others[7,8]. This can lead to consequences such as decreased mitochondrial membrane potential, decreased mitochondrial respiratory chain enzyme activity, impaired mitochondrial oxidative phosphorylation, and mitochondrial calcium overload, which in turn affects cardiomyocyte survival and function.

1.4 Calcium homeostasis

Calcium homeostasis refers to the dynamic balance of intracellular calcium ion concentration, which is important for maintaining normal systolic and diastolic function of cardiomyocytes.DOX can lead to mitochondrial calcium overload by inducing stress in the endoplasmic reticulum (ER)[9].The ER is an extensive intracellular network of membranes involved in Ca^{2+} storage and signalling.ER stress leads to the Ca^{2+} release from the ER lumen, which induces a sustained accumulation of Ca^{2+} in the mitochondrial matrix and triggers mitochondrial alterations such as permeability shifts, matrix swelling, Bax relocalisation, and cytochrome c release, which promotes apoptosis and the development of heart failure.

1.5 Autophagy

DOX can cause dysregulation of autophagy in cardiomyocytes, but whether DOX triggers or

inhibits autophagy remains controversial. Several studies have found that DOX promotes autophagy initiation and induces autophagic responses to eliminate damaged cytoarchitecture and mitochondria, and autophagy induction phenomena such as autophagosome formation and the conversion of microtubule-associated protein light chain 3 (LC3)-I to LC3-II were seen in DOX-applied mouse hearts. DOX upregulates a variety of autophagy proteins in the mouse heart including LC3-II, p62 and Beclin 1. However, other studies evaluating the downstream activity of autophagy have found that DOX inhibits autophagosome-lysosome fusion, lysosomal acidification, and blocks autophagic flow, leading to the accumulation of undegraded autophagosomes, which generates ROS and exacerbates cardiomyocyte injury and death. For mechanistic studies, DOX can inhibit transcription factor EB (TFEB), a regulator of autophagosome processing and lysosomal function, and TFEB deficiency inhibits lysosomal protein hydrolysis, leading to autolysosome accumulation and cell death.The mechanism of DOX-induced autophagy may be related to a variety of factors, such as the mTOR signalling pathway, AKT/Bcl-2 signalling pathway, FoxO3a transcription factor, etc[10,11]

1.6 Apoptosis

Apoptosis can be divided into two pathways, endogenous and exogenous, the former mediated by mitochondria and the latter by death receptors. Death receptors (DRs), including TNF receptor 1 (TNFR1), Fas, DR4 and DR5, are key mediators of apoptosis under physiological conditions. Individual DRs can be activated by their cognate ligands TNFα, Fas ligand (FasL), and TNF-related apoptosis-inducing ligand (TRAIL), which are produced by various cell types (T-cells, natural killer cells) and are commonly found in the bloodstream and the tissue microenvironment.TRAIL also selectively binds to DR4 and DR5, which are expressed on the cell surface.The connection of DRs induces the assembly of the death-inducing signalling complex (DISC), which triggers the activation of the cysteine asparaginase cascade, the cleavage of cellular proteins and ultimately apoptosis of the target cell[12].Induction of death receptors in cardiomyocytes may be a key mechanism of DIC[13][30].DOX induces apoptosis in cardiomyocytes by mechanisms that may involve multiple signalling pathways such as ERKS/p53, PI3K / AKT / mTOR, etc[14].

2. Novel Targets and Strategies for DIC

In recent years, with the deepening of DIC research, some novel targets and signalling pathways have been discovered and explored, such as the CRTH2 receptor, Nrf2 signalling pathway.

2.1 CRTH2 receptor

Activation of CRTH2 specifically promotes ER stress-induced cardiomyocyte apoptosis through a caspase-12-dependent pathway. m-Calpain blockade prevents CRTH2-mediated cardiomyocyte apoptosis in response to ER stress by inhibiting caspase-12 activity. CRTH2 couples with Gaq to trigger intracellular Ca2+ fluxes in cardiomyocytes while activating the m -calpain/caspase-12 cascade.CRTH2 deficiency attenuated hypoxia or DOX-induced apoptosis in cardiomyocytes[15]. Therefore, inhibition of CRTH2 receptor or its downstream molecules could attenuate Doxorubicin-induced myocardial injury and dysfunction.

2.2 Nrf2 signalling pathway

Nrf2 has long been recognised as an antioxidant and has a very high antioxidant capacity[16].DOX induces oxidative stress in cardiomyocytes by inhibiting the

SIRT1/LKB1/AMPK/Nrf2 signalling pathway, HSP20/AKT/GSK3β/FYN/Nrf2 signalling pathway[17,18];inhibits autophagy by suppressing Nrf2 expression[19]; and induces cardiomyocyte apoptosis by inhibiting upstream of the PI3K / AKT signalling pathway and P38/MAPK to induce cardiomyocyte apoptosis[20,21]; and inducing iron death in cardiomyocytes by regulating the expression of p62 and thereby inhibiting the expression of Nrf2[22], and SIRT1 may be one of the key components in the inhibition of Nrf2-induced iron death by DOX.The SIRT3/Nrf2 signalling pathway is involved in Doxorubicin-induced cardiomyocyte pyroptosis[23], and inhibition of the PI3K/AKT/Nrf2/p38/NF-κB p65 axis may be related to the pathway of Doxorubicin-induced cardiomyocyte inflammation[24]. Thus, it is evident that the pathogenesis of DIC is closely related to the inhibition of the Nrf2 signalling pathway, and therefore targeted activation of the Nrf2 signalling pathway is an important therapeutic strategy for DIC.

2.3 SIRTs protein family

Sirtuins (SIRTs) are a class of NAD+-dependent histone deacylases that regulate numerous key signalling pathways in prokaryotic and eukaryotic organisms and are involved in many biological processes such as cell survival, proliferation, apoptosis, senescence, DNA repair, oxidative stress and cellular metabolism. In addition to the above discussion that SIRT1 may be involved in DOX inhibition of Nrf2-induced iron death and SIRT3 in Doxorubicin-induced cardiomyocyte pyroptosis, it has been demonstrated that SIRT1 can protect the heart from DOX-induced toxicity by disrupting the interaction between sestrin 2 (SESN2) and mouse double minute 2 (MDM2) in order to reduce ubiquitination of SESN2. heart from DIC[25].Sirt6 can reduce Fas-FasL-mediated apoptosis and necrosis by up-regulating endogenous antioxidants as well as inhibiting oxidative stress and cell death signalling pathways that are dependent on ROS-stimulated p53 transcriptional activation[26]. In addition, SIRT6 enhances mitochondrial biogenesis and mitochondrial autophagy through deacetylation and inhibition of Sgk1. SIRT6 overexpression orchestrates the metabolic remodelling from glycolysis to mitochondrial respiration during Doxorubicin treatment, which is more favourable to cardiomyocyte metabolism and thus protects cardiomyocytes from Doxorubicin-induced energy deficiency[27].

3. Chinese medicine treatment of DIC

3.1 Scutellaria baicalensis

Baicalin (BA) is one of the main active components of Scutellaria baicalensis, which possesses a variety of biological activities such as antioxidant, anti-inflammatory and anti-tumour activities. It was found that by exploring the effects of DOX and baicalin on rat heart function, TLR4/IκBα/NFκB signalling pathway and related inflammatory indexes and by silencing or overexpressing TLR4 in cellular experiments, it was demonstrated that baicalin could achieve anti-inflammatory effects and ultimately inhibit DIC by modulating the TLR4 / IκBα / NFκB signalling pathway[28]. It was also demonstrated that BA inhibited gene overexpression of cardiac TLR4 and subsequently prevented Dox-induced elevation of cardiac NF-κB and IL-1β. BA also significantly reduced Dickkopf-1 (DKK1) levels in the heart and increased Wnt/β-catenin levels. Indicating that BA also achieves cardioprotective effects in the heart by inhibiting DKK1 activation of the protective Wnt/β-catenin signalling pathway[29].

3.2 Danshen

Tanshinone IIA (TSIIA) is one of the main active ingredients of Salvia miltiorrhiza, which has a

variety of biological activities such as antioxidant, anti-inflammatory and anticoagulant. It was found that TSIIA could protect cardiomyocytes from Doxorubicin-induced apoptosis by reducing the amount of cleaved caspase-3 and cytoplasmic cytochrome c and increasing the expression of BcL-x(L), partly through the Akt signalling pathway [30]. In addition, TSIIA restored autophagic flux by promoting autophagic lysosomal degradation and autophagosome formation through the up-regulation of Beclin1 and LAMP1, suggesting that TSIIA protects DIC by promoting autophagy through the Beclin1/LAMP1 signalling pathway[31].TSIIA also induced the expression of death structural domain-associated proteins (DAXX), p-ERK1/2 and p-MEK expression, inhibits the expression of cleaved caspase-8, p-P38 and cleaved caspase-3, activates the DAXX/MEK/ERK1/2 pathway and inhibits apoptosis in cardiomyocytes.

3.3 Astragalus

Astragaloside IV (AS-IV) is one of the main active ingredients of Astragalus membranaceus. Oxidative stress as an important mechanism of DIC and NADPH oxidase (NOX) plays an important role in its progression.Among the NOX family members, only NOX2 and NOX4 are expressed in the heart. It was found that AS-IV can downregulate NOX2 and NOX4 levels to ameliorate DOX-induced oxidative stress[32]. In addition, AS-IV can inhibit apoptosis through activation in the PI3K / Akt signalling pathway.AS-IV can also activate the Nrf2 signalling pathway and increase GPx4 expression to fight against iron death in order to achieve its protective effect against myocardial fibrosis[33].

3.4 Compound Danshen Drop Pills

Compound Danshen Drop Pills(CDDP) is a traditional Chinese medicine produced by combining traditional Chinese medicine and modern medical technology. It contains three herbs, Danshen, Panax notoginseng and Bingpian,it is now widely used in clinical practice for the prevention and treatment of myocardial infarction and other cardiovascular diseases, with the effects of activating blood circulation, removing blood stasis, nourishing blood and calming the mind.Recent studies have shown that CDDP has a significant inhibitory effect on DIC. First, CDDP significantly inhibited DOX-activated TGFβ1, COL1A2, COL3A1, αSMA, and MMP9. In addition, CDDP significantly reduced DOX-activated serum TNFα levels and its expression in the heart, suggesting that CDDP can reduce myocardial cardiac fibrosis and inflammation by inhibiting the expression of pro-fibrotic and pro-inflammatory molecules. Second, CDDP antagonised DOX-induced oxidative stress by reducing ROS and FFA production through activation of SOD1, p-AMPK and NRF2 expression [34].

4. Conclusions and outlook

This paper analyses the mechanism of Doxorubicin cardiotoxicity from multiple perspectives, and discusses some novel intervention targets and strategies, as well as some monomers and combinations of traditional Chinese medicines with preventive and curative effects, which provide a certain reference value for the in-depth understanding of the nature of Doxorubicin cardiotoxicity and for the search of effective preventive and curative methods. Although some targets and strategies against Doxorubicin cardiotoxicity have been proposed and validated, it is still incomplete to reveal its mechanism at the molecular level. Mechanistic studies at the molecular level of TCM provide a scientific basis for its treatment of DIC, but how to optimise the proportion and dosage of TCM monomers and compound formulas to improve their efficacy in treating DIC may be one of the future research directions. Therefore, it is necessary to further strengthen the

basic research and clinical trials in the future to explore more effective and reliable means of prevention and treatment to contribute to the overcoming of Doxorubicin cardiotoxicity.

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