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Chapter

Strategies to Treat Pulmonary Hypertension Using Programmed Cell Death-Inducing Anti-Cancer Drugs without Damaging the Heart

Yuichiro J. Suzuki, Yasmine F. Ibrahim, Vladyslava Rybka, Jaquantey R. Bowens, Adenike S. Falade and Nataliia V. Shults

Abstract

Pulmonary arterial hypertension (PAH) is a fatal disease without a cure. By the time patients are diagnosed with PAH, thickening of pulmonary arterial (PA) walls and the narrowing of vascular lumen have already developed due to the abnormal growth of pulmonary vascular cells, contributing to the elevated pulmonary vascular resistance and the right ventricle (RV) damage. Therefore, agents that eliminate excess pulmonary vascular wall cells have therapeutic potential, and the apoptosis-based therapy using anti-cancer drugs may be promising for the treatment of PAH. However, cell death agents could also exert adverse effects including cardiotoxicity, complicating the development of such therapies for PAH patients who already have the damaged heart. We tested the concept that programmed cell death-inducing anti-cancer drugs may reduce the PA wall thickening using rat models of PAH. We found that: (i) The treatment of PAH animals with anthracycline-, proteasome inhibitor- or Bcl-2 inhibitor-classes of anti-cancer drugs after the pulmonary vascular remodeling had already developed resulted in the reversal of PA wall thickening and opened up the lumen; (ii) These effects were accompanied by the apoptosis of PA wall cells in PAH rats, but not in normal healthy rats, suggesting the anti-cancer drugs selectively kill remodeled vascular cells; (iii) The RV affected by PAH was not further damaged by anthracyclines or proteasome inhibitors; (iv) While the left ventricle (LV) was damaged by these drugs, we identified cardioprotective agents that protect the heart against drug-induced cell death without affecting the efficacy to reverse the PA remodeling; and (v) docetaxel, not only reversed pulmonary vascular remodeling without exerting RV or LV toxicity, but also repaired the RV damage caused by PAH. Thus, the inclusion of programmed cell death-inducing anti-cancer drugs should be considered for treating PAH patients.

Keywords: anti-cancer drugs, apoptosis, autophagy, heart, programmed cell death, pulmonary hypertension, vascular remodeling

1. Introduction

Pulmonary arterial hypertension (PAH) is a fatal disease that can affect both females and males of any age including children. If untreated, increased pulmonary vascular resistance results in right heart failure and kills patients within several years [1, 2]. Even with the currently available therapeutic drugs that are mainly vasodilators, the survival duration of the patients remains unacceptably short [3, 4]. It has been reported that the median survival for patients diagnosed with PAH is 2.8 years from the time of diagnosis (3-year survival: 48%) if untreated [5, 6]. Even with currently available therapies, only 58–75% of PAH patients survive for 3 years [7–10]. PAH is a progressive disease, and by the time patients are diagnosed, thickening of pulmonary artery (PA) walls and the narrowing of vascular lumen have already developed due to the abnormal growth of pulmonary vascular cells, contributing to the elevated pulmonary vascular resistance and the right ventricle (RV) damage. Therefore, agents that eliminate excess pulmonary vascular wall cells have therapeutic potential, and we hypothesize that the programmed cell death-based therapy using anti-cancer drugs would help treat PAH patients [11]. However, cell death agents could also exert adverse effects including cardiotoxicity, complicating the development of such therapies for PAH patients with the already damaged heart.

2. Anti-cancer drugs reverse pulmonary vascular remodeling

In our earlier study, we found that an anthracycline anti-cancer drug daunorubicin (DNR) is an effective agent that can cause apoptosis of cultured PA smooth muscle cells (PASMCs) [11, 12]. Based on these results, we hypothesized that the administration of DNR to rats would result in the reversal of pulmonary vascular remodeling. In these experiments, Sprague-Dawley (SD) rats were treated with chronic hypoxia (10% oxygen) for 2 weeks to promote the thickening of PA medial walls. After the PA wall thickening was developed, rats were injected with DNR and maintained in the hypoxia condition for 3 days. As shown in hematoxylin and eosin (H&E) stain images of **Figure 1A**, DNR effectively reduced the PA wall thickness [13]. Similarly, in this study, another class of anti-cancer drugs, proteasome inhibitors such as MG132 and bortezomib (**Figure 1B**) also reduced the PA wall thickening in the chronic hypoxia model of pulmonary hypertension (PH) in rats [13].

An animal model, in which SD rats are injected with SU5416 and exposed to hypoxia promoting severe PAH with pulmonary vascular lesions resembling those of humans [14], has become a gold standard to study PAH [15]. The experimental design often involves a single subcutaneous injection of SU5416, followed by subjecting the animals to chronic hypoxia for 3 weeks. Subsequently, the animals are kept in normoxia, and severe PAH and pulmonary vascular remodeling are progressively developed. We found that programmed cell death-inducing anti-cancer drugs reversed pulmonary vascular remodeling in this model of PAH as well. **Figure 1C** shows the results of our experiments, in which another proteasome inhibitor, carfilzomib (CFZ) injected 4 times over two weeks after the pulmonary vascular remodeling was developed effectively reduced the PA wall thickness in PAH rats [16]. Proteasome inhibition-dependent reversal of pulmonary vascular remodeling occurred through the reduction of both intimal and medial wall thickening, suggesting that both endothelial cells and smooth muscle cells (SMCs) can be affected by these anti-cancer drugs [13].

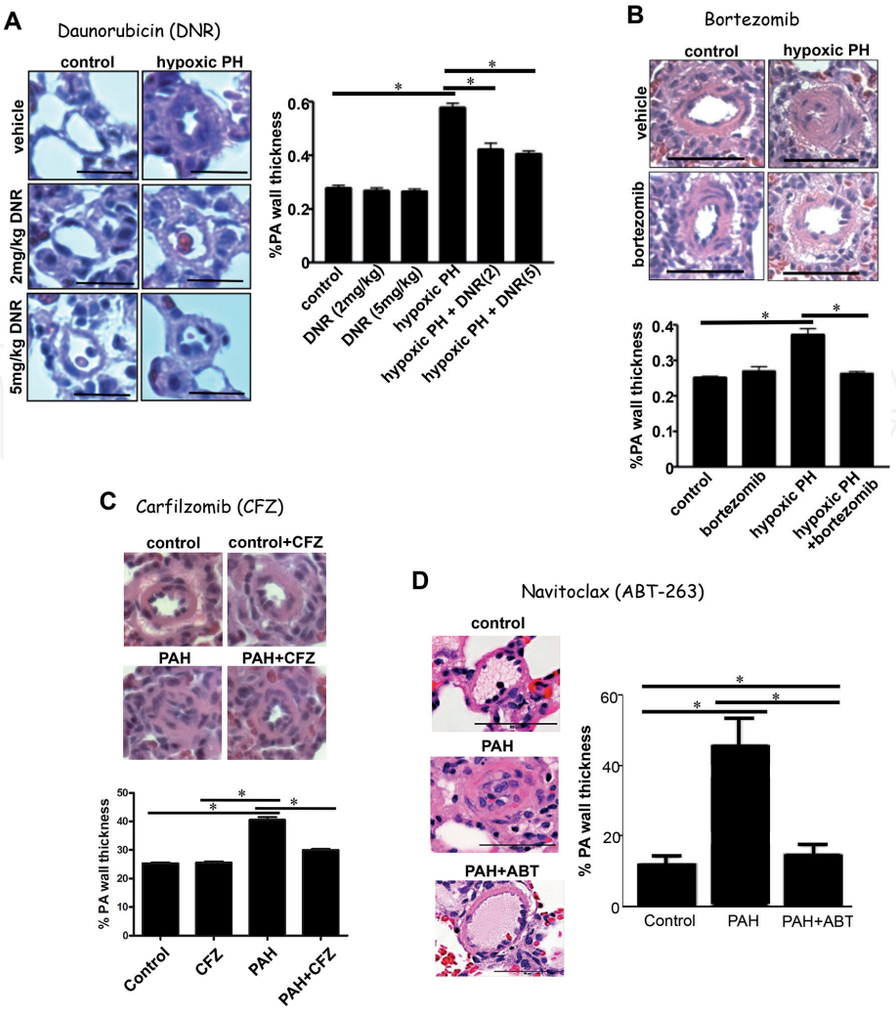


Figure 1.
*Effects of programmed cell death-inducing anti-cancer drugs on pulmonary vascular remodeling. (A & B) SD rats were treated with chronic hypoxia for 2 weeks to produce pulmonary vascular thickening and injected with DNR or bortezomib. Rats were then placed back in the hypoxic environment. Three days after the injection, lungs were harvested and H&E staining was performed (Adapted from Ibrahim et al. [13] with permission). (C & D) SD rats were subjected to SU5416/hypoxia to promote PAH. After pulmonary vascular remodeling was developed, rats were injected with CFZ or navitoclax twice a week for 2 weeks. Lungs were harvested and H&E staining was performed (Adapted from Wang et al. [16] and Rybka et al. [17] with permission). Bar graphs represent means ± SEM of % PA wall thickness. * denotes that the values are significantly different from each other at $P < 0.05$.*

While anthracyclines such as DNR and proteasome inhibitors are effective inducers of apoptosis of PASMCs [11, 13, 16], these agents could exert other biologic actions. Thus, we tested the effects of a more 'pure' apoptosis inducer, navitoclax (ABT-263) that inhibits anti-apoptotic proteins Bcl-2 and Bcl-x_L. We found that this drug also reversed PA remodeling in SD rats as well as in Fischer rats with PAH promoted by SU5416 + hypoxia (**Figure 1D**; [17]). The reversal of pulmonary vascular remodeling by navitoclax was also recently reported by van der Feen et al. [18] in a different experimental model of PAH in rats.

These results provided important information, in live experimental animals, showing that programmed cell death-inducing anti-cancer drugs are capable of reversing pulmonary vascular remodeling in multiple models of PH. While this knowledge established a basis for exploring whether causing the death of pulmonary vascular cells clinically benefits PAH patients, it also generated many questions that need to be addressed.

3. Susceptibility of normal and diseased cells toward apoptosis-inducing anti-cancer drugs

One question is whether both the proliferative synthetic phenotype and the differentiated contractile phenotype of PASMCs are killed by these drugs. It is preferable that only abnormally grown cells are killed, as it is important to preserve contractile SMCs that are needed for the pulmonary circulatory system to function.

The examination of PAs from rats treated with DNR by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining, which detects apoptotic cells, demonstrated that only remodeled PAs of rats with PH exhibited apoptotic cells, but not healthy control rats (**Figure 2A**; [13]). Similar results were obtained in the analysis of cleaved caspase-3 as an indication of the occurrence of apoptotic cells by Western blotting. As shown in **Figure 2B**, PAs from rats treated with chronic hypoxia to promote PH and subsequently treated with DNR exhibited significantly higher levels of cleaved caspase-3 compared to healthy rats injected

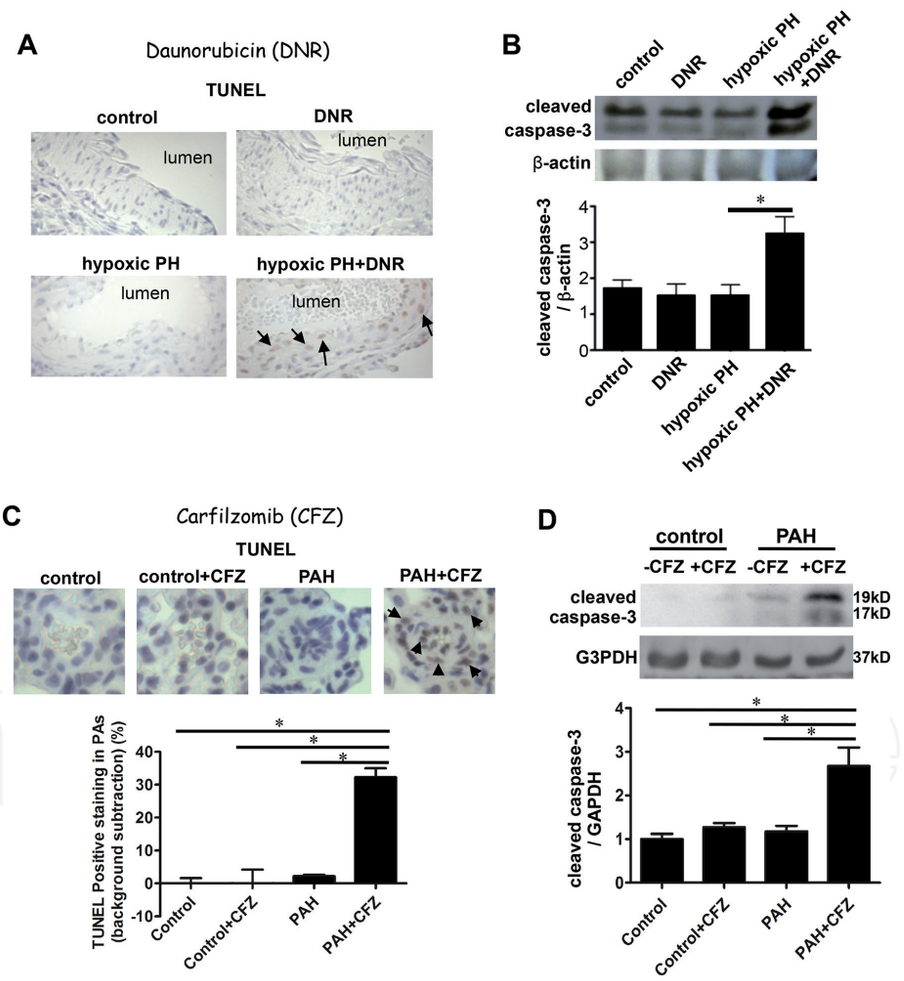


Figure 2.
*Effects of programmed cell death-inducing anti-cancer drugs on apoptosis. (A & B) SD rats were treated with chronic hypoxia for 2 weeks to produce pulmonary vascular thickening and injected with DNR. Rats were then placed back in the hypoxic environment. Three days after the injection, lungs were harvested and TUNEL staining and Western blotting with the cleaved caspase-3 antibody were performed to monitor apoptosis (Adapted from Ibrahim et al. [13] with permission). (C & D) SD rats were subjected to SU5416/hypoxia to promote PAH. After pulmonary vascular remodeling was developed, rats were injected with CFZ twice a week for 2 weeks. Lungs were harvested and TUNEL staining and Western blotting with the cleaved caspase-3 antibody were performed to monitor apoptosis (Adapted from Wang et al. [16] with permission). Bar graphs represent means ± SEM. * denotes that the values are significantly different from each other at $P < 0.05$.*

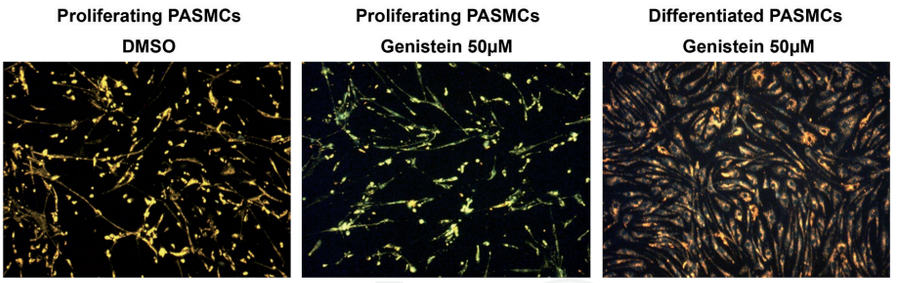


Figure 3.
Effects of genestein on proliferating and differentiated human PASMC apoptosis. Proliferating human PASMCs purchased from Cell Applications grown in Human SMC Growth Medium and differentiated PASMCs produced using the Human SMC Differentiation Medium were treated with genistein (50 μM). Apoptotic cells were identified by green fluorescence produced using the DePsipher Mitochondrial Potential assay.

with DNR [13]. These results revealed that unwanted abnormally grown pulmonary vascular cells can preferentially be killed by this anti-cancer drug.

Results shown in **Figure 2C** and **D** demonstrated that this increased susceptibility of pulmonary vascular cells in PH animals can also be seen with another anti-cancer drug. CFZ also caused the apoptosis in PAs of rats with PAH induced by SU5416/hypoxia, while no apoptosis signals were observed in control healthy rats treated with CFZ as monitored by TUNEL assay (**Figure 2C**) and Western blotting using the cleaved caspase-3 antibody (**Figure 2D**) [16].

We hypothesized that anti-cancer drugs preferentially kill the proliferating phenotype of SMCs over differentiated SMCs. Our experiments using cultured PASMCs showed that only proliferating SMCs, but not differentiated SMCs, were killed by DNR [13]. **Figure 3** shows similar experimental results when proliferating and differentiated human PASMCs were treated with genistein, a naturally occurring isoflavone. DePsipher Mitochondrial Potential assay (Trevigen, Gaithersburg, MD, USA) showed that green fluorescent apoptotic cells were only observed when proliferating PASMCs were treated with genistein, while differentiated PASMCs produced by using the Differentiation Medium (Cell Applications, Inc., San Diego, CA, USA) were resistant to be killed by the same concentration of genistein. These results demonstrate that proliferating PASMCs are more susceptible to undergo apoptosis compared to differentiated PASMCs, suggesting that apoptosis-inducing drugs eliminated unwanted proliferating PASMCs while preserving the contractile phenotypic cells with muscle functions.

4. Role of autophagic cell death

One interesting observation we came across in relation to the mechanism of PASMC killing by anthracycline- and proteasome inhibitor-classes of anti-cancer drug is that, in addition, to apoptosis, another programmed cell death mechanism, namely autophagic cell death is also involved. We initially found that autophagy of the cells is increased in PAs of PH rats treated with DNR [13]. Similar results were observed in cultured proliferating human PASMCs when cells were treated with DNR. Further, DNR-induced cell killing was attenuated when an autophagy mediator, LC3B, was knocked down [13]. CFZ-induced cell killing was also found to involve autophagy, and we further identified the role of tumor protein p53-inducible nuclear protein 1 (TP53INP1) in this mechanism [16].

5. The ability of the remodeled RV to cope with program cell death-inducing drugs

Drugs that promote programmed cell death are effective anti-cancer drugs, however, they also exert serious potentially life-threatening complications [19]. Cardiotoxicity is a major complication that accompanies the use of anti-cancer drugs especially anthracyclines. Since PAH patients already have the weakened heart, the use of these anti-cancer drugs would be considered to be contraindications. However, we found that the RV affected by PAH is remarkably resistant to drug-induced myocardial cell killing. As we characterized the RV of PAH rats injected with DNR to reverse PA remodeling as described above, we found that DNR administration to PAH rats did not influence the RV contractility or the RV structure [13]. This study also found that DNR did not promote apoptosis of cardiomyocytes in hypertrophied RV in rats with PH (**Figure 4A**; [13]). Similarly, CFZ that was found to effectively reverse PA remodeling did not cause apoptosis in the RV in SU5416/hypoxia model of PAH in rats (**Figure 4B**; [16]). These are highly significant findings revealing that the RV affected by PAH is resistant to DNR and CFZ, drugs that are known induce cardiotoxicity and cardiomyocyte killing in the normal heart, providing evidence that the clinical use of these anti-cancer drugs in PAH patients may not be contraindications.

By contrast, bortezomib was found to promote apoptosis in both RV and left ventricle (LV) of rats with PH induced by monocrotaline [20]. Also, navitoclax (ABT-263; an inhibitor of anti-apoptotic proteins, Bcl-2 and Bcl-xL), not only

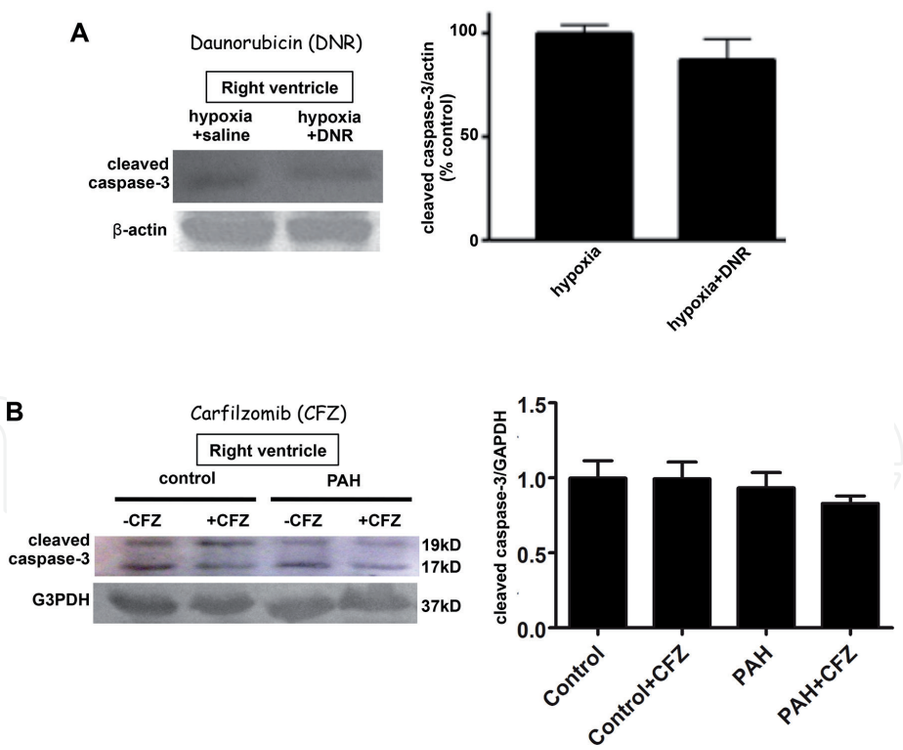


Figure 4.
Effects of programmed cell death-inducing anti-cancer drugs on the RV affected by PAH. (A) SD rats were treated with chronic hypoxia for 2 weeks to produce pulmonary vascular thickening and injected with DNR. Rats were then placed back in the hypoxic environment. Three days after the injection, RV tissues were harvested and Western blotting with the cleaved caspase-3 antibody was performed to monitor apoptosis (Adapted from Ibrahim et al. [13] with permission). (B) SD rats were subjected to SU5416/hypoxia to promote PAH. After pulmonary vascular remodeling was developed, rats were injected with CFZ twice a week for 2 weeks. RV tissues were harvested and Western blotting with the cleaved caspase-3 antibody were performed to monitor apoptosis (Adapted from Wang et al. [16] with permission). Bar graphs represent means ± SEM. All the values were not significantly different from each other at $P < 0.05$.

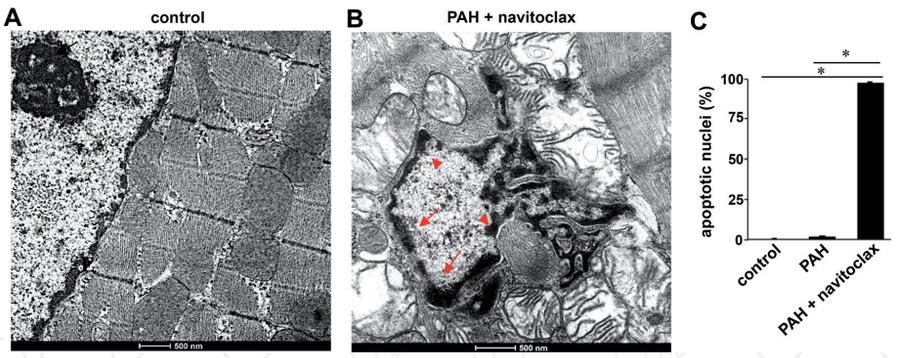


Figure 5.
*Navitoclax promotes cardiomyocyte apoptosis in the RV affected by PAH. (A) The normal RV structure of RV cardiomyocytes as monitored by transmission electron microscopy. Magnification ×16,000. (B) SD rats were subjected to SU5416/hypoxia to promote PAH. After pulmonary vascular remodeling was developed, rats were injected with navitoclax twice a week for 2 weeks as described in Rybka et al. [17]. RV tissues were harvested and a transmission electron microscope was used to analyze the apoptotic nuclei. Bar graphs represent means ± SEM. * denotes that the values are significantly different from each other at $P < 0.05$. Transmission electron microscopy studies were performed as described in Shults et al. [32].*

caused apoptosis in the remodeled PA [17], but also promoted apoptosis in RV myocytes in PAH rats. **Figure 5** shows the transmission electron microscopy images of normal SD rat RV myocytes (**Figure 5A**) and RV myocytes from PAH SD rats treated with navitoclax exhibiting signs of apoptosis (**Figure 5B**). The nuclei PAH rats treated with navitoclax underwent the fragmentation with dramatic changes in the nuclear chromatin with the segregated heterochromatin that distributed preferentially within the nuclear envelope as sharply defined clumped bodies (**Figure 5B**, red arrowheads). The quantification of apoptotic nuclei revealed that the most of RV myocytes in PAH rats became apoptotic when treated with navitoclax (**Figure 5C**).

These results suggest that, while three classes of anti-cancer drugs have so far been found to be effective in reversing PA remodeling, hypertrophied RV myocytes are only resistant to DNR and CFZ, while Bcl-2/Bcl-x_L inhibition seems target downstream of apoptotic pathway thus escapes from the resistance to cardiomyocyte killing. Whether the RV damaging effects of bortezomib in PAH rats [20] is specific to the model induced by monocrotaline that can exert non-specific pathophysiologic actions need further investigations, however, the data so far do not support the use of bortezomib in the PAH treatment. CFZ that is considered to be a safe alternative to bortezomib in cancer therapy [21] and is a more selective and irreversible inhibitor of the chymotrypsin-like activity of the 20S proteasome [22, 23] could be more promising.

6. Cardioprotective agents to cope with LV myocyte death by anti-cancer drugs

Our laboratory previously found a cell-signaling pathway for the downregulation of Bcl-x_L/Bcl-2 that results in the apoptosis of cardiomyocytes [24]. This pathway was found as a consequence of our laboratory cloning the promoter region of the GATA4 transcription factor that regulates gene transcription of Bcl-x_L and Bcl-2. We found that CBF/NF-Y binding to the CCAAT box of the Gata4 promoter is inhibited by DNR through the activation of p53 in cardiomyocytes [24], but not in PASMCs [13]. Thus, we hypothesized that p53 inhibitors would protect the heart against cardiotoxicity induced by anti-cancer drugs without affecting the efficacy of these drugs to reverse PA remodeling.

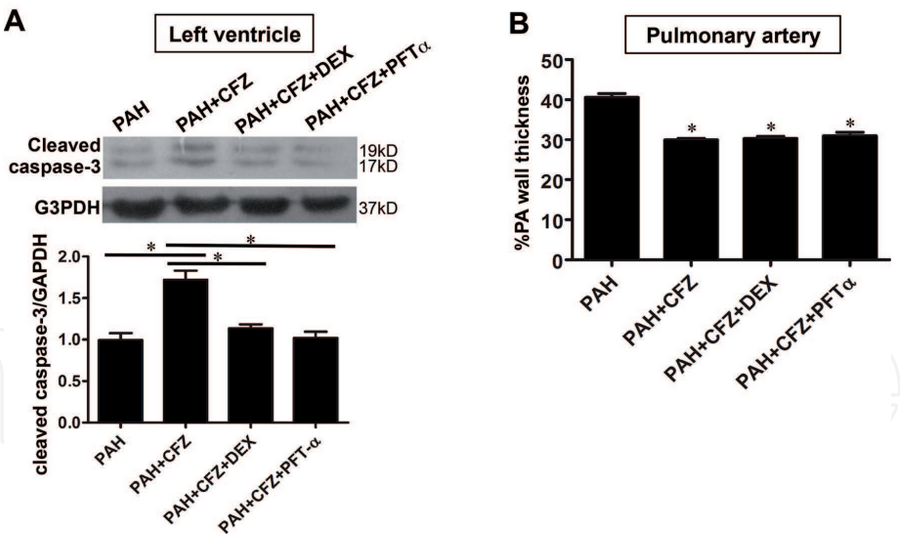


Figure 6.
*Dexrazoxane (DEX) and pifithrin-α (PFT-α) protects the LV from CFZ-induced apoptosis without affecting the efficacy of CFZ in reversing PA remodeling. (A) PAH rats (SU5416/hypoxia) were divided into 4 groups. DEX or PFT-α was injected intraperitoneally along with CFZ, twice a week for two weeks. Rats were then sacrificed 3 days after the last injection. LV tissues were homogenized, and subjected to Western blotting for the cleaved capase-3 formation. The bar graph represents means ± SEM. * denotes that the values are significantly different from each other at P < 0.05. (B) The reduction of remodeled PA thickness induced by CFZ was not affected by DEX or PFT-α by analyzing H&E staining. The bar graph represents means ± SEM. * denotes that the values are significantly different from the PAH value at P < 0.05. (Adapted from Wang et al. [16] with permission).*

In our study of CFZ as described above, we found that this proteasome inhibitor is effective in reversing PA remodeling and that the RV affected by PAH is resistant to CFZ toxicity [16]. However, as expected from the earlier cancer studies, CFZ did cause the cardiomyocyte apoptosis in the LV of PAH rats (**Figure 6A**). As a support for our hypothesis, this CFZ-induced apoptosis of LV cardiomyocytes was inhibited by a p53 inhibitor, pifithrin-α in PAH rats (**Figure 6A**), while this cardioprotective agent did not interfere with CFZ reducing the PA wall thickening (**Figure 6B**). Interestingly, we found that a clinically used cardioprotective drug, dexrazoxane, also protected that LV of PAH rats from CFZ toxicity without affecting the reversal of PA remodeling. Further investigations are needed to determine whether these actions of dexrazoxane involve p53. Nevertheless, these results suggest including dexrazoxane or a p53 inhibitor to protect the LV against drug-induced damage while treating PAH patients with anti-cancer drugs.

7. Docetaxel as a fascinating drug that reduces pulmonary vascular wall thickening and repairs the damaged right ventricle

Since experiments described above provided results that support the use of anti-cancer drugs to reverse pulmonary vascular remodeling, we further searched for other drugs that could be useful. In an effort to find effective drugs that preferentially kill proliferating PASMCs, we screened various drugs [25]. We found that docetaxel (a taxane class of anti-cancer drugs that stabilizes and inhibits microtubules) effectively killed proliferating human PASMCs, but not differentiated human PASMCs in culture [25]. As we tested docetaxel for reversing pulmonary vascular remodeling in the SU5416/hypoxia model of PAH, we found that this drug indeed was effective in reducing thickened pulmonary vascular walls (**Figure 7A**). Effects were similar to anthracycline-, proteasome inhibitor-, and Bcl-2/Bcl-x_L

inhibitor-classes of drugs. As described above, we found that DNR and CFZ did not have adverse effects on the hypertrophied RV in PAH rats while Bcl-2/Bcl-x_L inhibition resulted in the apoptosis of RV myocytes. Docetaxel also did not exhibit adverse effects on the hypertrophied RV in PAH rats. Moreover, this drug repaired damaged RV caused by PAH. In SU5416/hypoxia model of PAH, the RV was found to have significant cardiac fibrosis as shown in the blue stain of Masson's trichrome staining in **Figure 7B**. Remarkably, these fibrotic lesions were eliminated by the treatment of PAH rats with docetaxel (**Figure 7B**; [25]).

These results suggest that docetaxel is an effective drug that can reverse pulmonary vascular remodeling and at the same time it can also repair the damaged RV caused by PAH at least in SD rats treated with SU5416/hypoxia. Another taxane drug, paclitaxel has also been shown to attenuate pulmonary vascular remodeling in rodent models of PAH induced by monocrotaline or SU5416/hypoxia [26–30]. However, the ability of paclitaxel to repair the RV in PAH animals has not been reported. It is interesting to note that paclitaxel has been shown to improve cardiac function during ischemia in isolated rat and rabbit hearts [31], reinforcing the idea that taxanes have the capacity to promote cardiac repair.

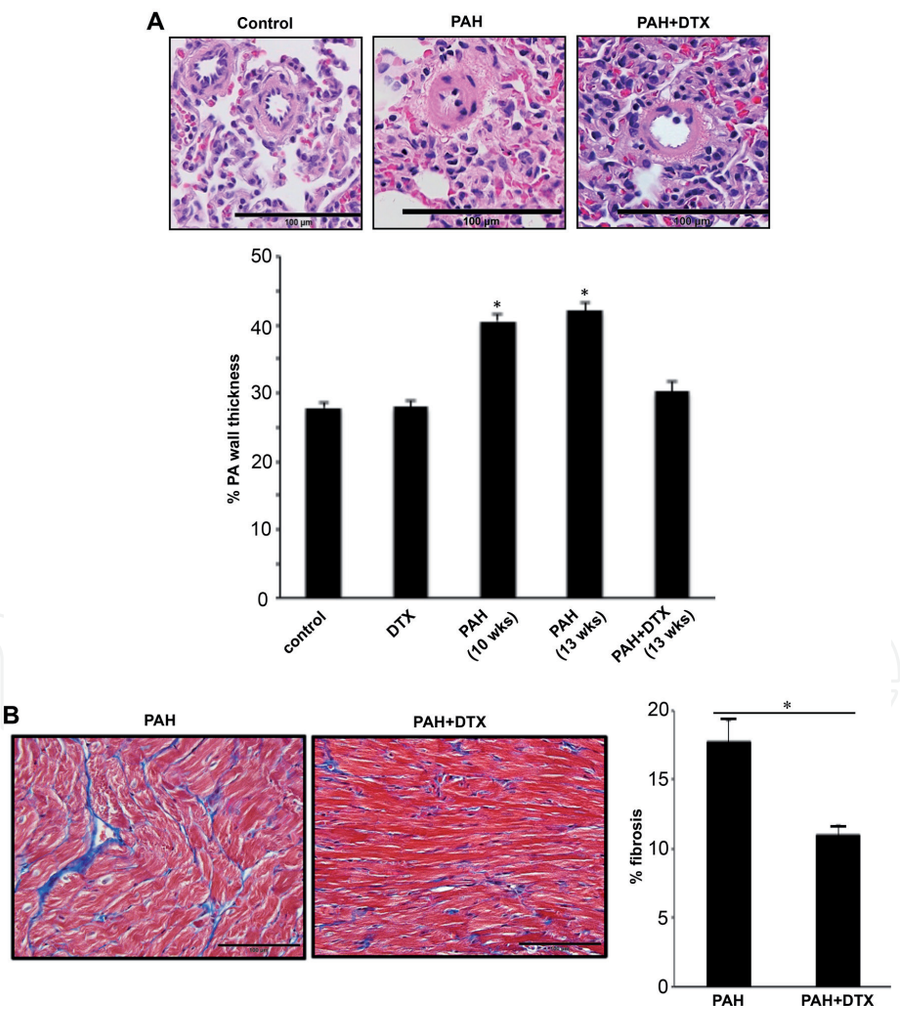


Figure 7.
*Docetaxel reverses pulmonary vascular remodeling and cardiac fibrosis in the RV in PAH rats. SD rats were subjected to SU5416/hypoxia to promote PAH. After pulmonary vascular remodeling was developed, rats were injected with DTX twice a week for 2 weeks. (A) Lungs were harvested and H&E staining was performed. The bar graph represents means ± SEM of % PA wall thickness. * denotes that the values are significantly different from each other at P < 0.05. (B) Heart tissues were harvested and Masson's trichrome staining was performed to monitor fibrosis. The bar graph represents means ± SEM of % fiborsis in the RV. * denotes that the values are significantly different from the PAH value at P < 0.05. (Adapted from Ibrahim et al. [13] with permission).*

8. Conclusions

We tested the concept that cell death-inducing anti-cancer drugs may reduce the PA wall thickening using rat models of PAH. We found that: (1) The treatment of PAH rats with anthracycline-, proteasome inhibitor- or Bcl-2/Bcl-x_L inhibitor-classes of drugs after pulmonary vascular remodeling had occurred resulted in the reversal of pulmonary vascular remodeling and opened up the lumen; (2) These effects were accompanied by the apoptosis of PA wall cells in PAH rats, but these drugs did not promote apoptosis in normal healthy rats, suggesting the anti-cancer drugs selectively kill remodeled vascular cells; (3) DNR, an anthracycline, and CFZ, a proteasome inhibitor, did not adversely affect the hypertrophied RV of PAH rats. (4) While the LV was damaged by CFZ, we identified cardioprotective agents (dexrazoxane and pifithrin-alpha) that can protect the heart against drug-induced cell death without affecting the efficacy of the drugs to reduce PA remodeling; (5) Docetaxel, a taxane class of anti-cancer drugs, not only reversed pulmonary vascular remodeling without exerting RV or LV toxicity, but also repaired the RV damaged caused by PAH. These findings from our laboratory as well as reports by other laboratories on the topic of the effects of programmed cell death-inducing anti-cancer drugs on remodeled PA and the RV affected by PAH in experimental animals are summarized in **Table 1**.

These results demonstrate that certain anti-cancer drugs effectively and selectively cause programmed cell death of abnormally grown cells in the remodeled pulmonary vasculature without adversely affecting the RV in rat models of PAH. Thus, the inclusion of programmed cell death-induced anti-cancer drugs may be promising for treating PAH patients. Human clinical trials of PAH treatment that test the effectiveness of these anti-cancer drugs as mono-therapies or combination therapies along with cardioprotective agents described here as well as already available vasodilators are warranted.

	Reduces remodeled PA	**Affects remodeled RV**
Daunorubicin, DNR (Anthracycline)	Yes	No effects
Carfilzomib, CFZ (Proteasome inhibitor)	Yes	No effects
Bortezomib (Proteasome inhibitor)	Yes	Apoptosis
Navitoclax, ABT-263 (Bcl-2/Bcl-x_L inhibitor)	Yes	Apoptosis
Docetaxel, DTX (Taxane; Microtubule inhibitor)	Yes	Repairs
Paclitaxel (Taxane; Microtubule inhibitor)	Yes	Unknown

Table 1.
Abilities of various anti-cancer drugs to affect PA and RV remodeling.

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Conflict of interest

None.

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