PS-1

Identification of Novel Therapeutic Targets for Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is characterized by histological changes in the distal pulmonary arteries. In addition to genetic considerations, many environmental factors are involved in the development of PAH. All of these factors constitute complex interactions that affect pulmonary vasculature in a multi-stage manner. Thus, the identification of genes, which cause the abnormal characteristics of PASMCs, should be useful for the development of novel therapies for PAH. The characteristics of PASMCs of PAH patients (PAH-PASMCs) are different from those of healthy controls, in terms of pro-proliferative and anti-apoptotic features, which are similar to those of cancer cells. These features of PAH-PASMCs may be caused by some unknown pathogenic genes that promote PAH. Since conventional pulmonary vasodilators have limited efficacy for the treatment of severe PAH, we have performed a series of screens and found novel therapeutic targets. Moreover, we performed a high-throughput screening of small molecules and identified inhibitors for the novel therapeutic targets. In this special session, we will discuss as to the recent progress of our translational research

PS-2

Japanese treatment goal of pulmonary artery hypertension

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Generally, it has been believed that pulmonary artery pressure in established pulmonary artery hypertension (PAH) could not be sufficiently decreased while keeping the cardiac output. Therefore, even now, the treatment goal of PAH indicated in European guideline is to keep the patients' condition without causing right ventricular failure. Until 2006, the treatment goal of PAH in Okayama medical center was just the bridging to lung transplantation. However, because of lack of donors, at least 5 years survival were necessary for PAH patients to be underwent lung transplantation. Thus, I treated the patients with slow continuous up titration of epoprostenol and finally, the dosage of epoprostenol reached extremely high dose. As a result, mean pulmonary artery pressure in many patients could be sufficiently decreased while keeping cardiac output and most of them could survive more than 10 years without lung transplantation. I changed the treatment goal of PAH to obtaining sufficient decrease of pulmonary artery pressure from 2006. To achieve this new treatment goal, rapid up titration of epoprostenol and combination treatment with other targeted drugs have been performed. Currently, 10 years survival rate of idiopathic/heritable PAH in Okayama has been reached 78%. This success would be owing to lack of donor, relatively small body size, and well established insurance system; all specific to Japan. I'd like to talk about this own Japanese treatment goal in this lecture.

PS-3

Hemodynamic Stress is Essential to Occlusive Lesions in PAH

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Background: A current leading hypothesis of the pathogenesis of PAH is that cancer-like cellular proliferation leads to the occlusive vascular lesions. However, it remains unknown whether hemodynamic stress is important in the development and maintenance of these lesions in PAH.
Methods and Results: We applied left pulmonary artery banding (LPAB) in SU5416/hypoxia/normoxia-exposed rats. The LPAB surgery to reduce hemodynamic stress to the left lung was done 1 week prior to and 5 weeks after the SU5416 injection. Histological analyses showed that the non-banded right lungs developed the occlusive lesions including plexiform lesions at 10 week after SU5416 injection. In contrast, LPAB not only prevented but also completely reversed the occlusive vascular lesions to normal levels. Perivascular inflammatory accumulation and nuclear factor-kB expressions were markedly reduced in the banded lungs.
Conclusions: Hemodynamic stress is prerequisite to the development and maintenance of cancer-like occlusive lesions. Our results support the concept why the maximal reductions in hemodynamic stress by up-front therapy dramatically improves the survival of severe PAH patients.

PS-4

Data from Registry of Japanese Patients with PAH

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Background:
The trend of the initial treatment strategy for pulmonary arterial hypertension (PAH) has changed from monotherapies to upfront combination therapies. This study aimed to analyze treatments and outcomes in Japanese patients with PAH by using data from the Japan PH Registry (JAPHR), which is the first organized multicenter registry for PAH in Japan.
Methods and Results:
We studied 189 consecutive patients (108 incident and 81 prevalent cases) with PAH in nine pulmonary hypertension centers enrolled from April 2008 to March 2013. We performed survival analyses and the association between upfront combination and hemodynamic improvement adjusting for baseline NYHA classification status.
Among the 189 patients, 1-, 2-, and 3-year survival rates were 97.0% (95%CI, 92.1–98.4), 92.6% (95%CI, 87.0–95.9), and 88.2% (95%CI, 81.3–92.7), respectively. In the incident cohort, 33% of the patients received upfront combination therapies. In this cohort, 1-, 2-, and 3-year survival rates were 97.6% (95%CI, 90.6–99.4), 97.6% (95%CI, 90.6–99.4), and 95.7% (95%CI, 86.9–98.6), respectively. Patients on upfront combination therapy were 5.27 (95%CI, 2.68–10.36) times more likely to show hemodynamic improvement at the first follow-up compared with monotherapy.
Conclusions:
Data from the JAPHR suggest the advantage of initial upfront combination therapy associated with improvement in hemodynamic status.