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Editorial Open Access

Targeting Epigenetic Changes for the Reprogramming of Vascular Walls in Pulmonary Arterial Hypertension, the Role of Histone Deacetylases and their Inhibitors

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Pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculature as defined by an elevated pulmonary vascular resistance (PVR) leading to a failure of the right heart and ultimately death [1]. Although the overall 5-year survival for PAH has significantly increased in the past years, none of the approved therapies have shown an ability to cure the disease. Current available treatments are limited, expensive, and often associated with significant, side effects. As such, furthering our understanding of the mechanisms underlying PAH development is important to improve patient management and outcomes.

A number of evidence have shown that cellular and molecular changes occur in the pulmonary arteries in response to chronic hypoxic exposure [1,2], and primary lung diseases including chronic obstructive pulmonary disease, cystic fibrosis, etc. are associated with the presence of chronic hypoxia. In PAH, the pulmonary arteries (PAs) exhibit pathological proliferative vascular remodeling related to medial and adventitial thickening of pulmonary arterial walls. The excessive proliferation of smooth muscle cells as well as the accumulation of fibroblasts and myofibroblasts plays an important role in the medial and adventitial thickening respectively.

Epigenetics describes that heritable changes in gene expression or cellular phenotype are caused by mechanisms other than changes in the underlying DNA sequence. Histone modification is one of the predominant epigenetic phenomena. It selectively modulates gene expressions that control many biological processes including cell proliferation. Histone deacetylases (HDACs) remove an acetyl group from lysine residues of target proteins to regulate a number of cellular processes. There are 18 HDAC enzymes which are identified and grouped into four classes. Class I, II, and IV share sequence similarity and are dependent on Zn2+ for enzymatic activity, whereas the class III sirtuins act through a distinct NAD+-dependent mechanism.

Pulmonary vascular remodeling (PAR) is a characteristic pathological change of PAH. The development of PAR involves all layers of the vessel wall. It has been reported that adventitial fibroblasts in the pulmonary hypertensive vessel wall exhibit a hyper proliferative, inflammatory, and invasive phenotype. Hypoxia-induced PAR is characterized by the emergence of a distinct adventitial fibroblast population. This population exhibits a constitutively activated, pro-inflammatory phenotype that is capable of inducing recruitment, retension and pro-inflammatory activation of monocytes/microphages. Stenmark's group has recently demonstrated that pulmonary adventitial fibroblasts from chronically hypoxic hypertensive calves (PH-Fibs) expressed a constitutive and persistent proinflammatory phenotype. The proinflammatory phenotype of PH-Fibs was associated with epigenetic alterations as demonstrated by increased activity of HDACs. Importantly, a reversal of this proinflammatory phenotype can be achieved with the use of class I HDAC inhibitors [3].

Another hallmark feature of PAR is excessive smooth muscle cell proliferation leading to medial thickening. In our high altitude long-term (LTH) sheep model, an obvious pulmonary arterial remodeling was observed. We found that the level of global histone acetylation was significantly decreased in LTH fetus PAs, and it was accompanied by the loss of the cyclin-dependent kinase inhibitor, p21, as opposed to the control. The treatment of the pulmonary arterial smooth cells (PASMC), isolated from LTH fetal lung, with a class I HDAC inhibitor markedly decreased their proliferation rate in part due to an increased expression of p21 at both the RNA and protein level. Interestingly, a class II HDAC inhibitor also showed an inhibitory effect on cell proliferation when used with a relative higher concentration. However, a class III inhibitor exhibited no effect on cell proliferation [4]. These findings suggested that epigenetic alterations caused by chronic hypoxia led to fetal PASMC proliferation and vessel remodeling as associated with vascular proliferative disease, and that this process is regulated by p21. This is consistent with a previous study which showed that a p53 gene deficiency decreased p21 expression levels that eventually resulted in hypoxia-induced PAH and vascular remodeling in mice [5].

The above studies correlate with in vivo data showing that small molecules (MGCD0103 and MS-275) that selectively block class I HDACs reduce hypoxia-induced PAH in a manner that associates with a blunted medial thickening of PAs and a reduced proliferation of PASMC in these vessels [6]. These findings support a unique role for HDACs as important targets for PAH, and highlight the potential of isoform-specific HDAC inhibitors for the treatment of cardiovascular diseases.

Although the knowledge of cellular and molecular basis of PAH is still limited, there is more evidence showing that epigenetic mechanisms could be involved in the development of PAH. Epigenetic modifications offer the prospect of "reverse chromatin remodeling", leading to a decrease in vascular remodeling. The epigenetic mechanisms of histone acetylation may have significant mechanistic and therapeutic implications in human PAH and specific HDACs may be used as new targets for therapy in vascular disease.

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