Editorial

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Beyond Vasodilator: Anti-Apoptotic Effect of Endothelin Receptor Antagonist

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Treatment of pulmonary arterial hypertension (PAH) has changed with development of PAH targeted therapy, which includes use of specific vasodilator in pulmonary arterial system. Bosentan is an endothelin receptor antagonist (ERA) and vasodilator that was the first approved oral drug for PAH treatment. The clinical benefit of bosentan has been established in several multicenter clinical trials[1)2)] and shown to develop slowly over several months. Therefore, beyond its vasodilator effect, the effect of ERA on PAH progression has been investigated.

Pathology of pulmonary artery in PAH patients shows vascular smooth muscle proliferation and obliteration of pulmonary vessels. Endothelial dysfunction is commonly found, and inflammatory response and endothelial cell apoptosis have also been reported. After apoptosis of normal endothelial cell line, surviving cells proliferate. This abnormal proliferation forms unique plexiform lesions that obliterate arterioles and capillaries at the end stage of disease. Vascular smooth muscle cells are prone to hyperplasia and unbalanced apoptosis (decreased apoptosis) leads to hypertrophy of the vessel wall.

Endothelin (ET) is produced in endothelial cells of various tissues. Especially, ET-1 is predominantly expressed in pulmonary circulation. ET-2 mainly expressed in the kidney and ET-3 in the brain and intestine.[3)] ET is secreted from the abluminal side of the cells towards the adjacent vascular smooth muscle cells. There are two types of ET receptor including ET_A and ET_B. ET_A is located in pulmonary vascular smooth muscle cells where it mediates vasoconstriction through inositol trisphosphate (IP_3) formation and release of intracellular calcium. The ET_A receptor is associated with proliferation of vascular smooth muscle cells in pulmonary arteries. In PAH patients, expression of the ET_A receptor is increased and is associated with vasoproliferation. Inflammation also plays an important role in PAH patients and ET_A is elevated in this setting.

Imbalance between proliferation and apoptosis in vascular smooth muscle cells is associated with vascular hypertrophy in PAH.[4)] However, before initiation of vascular hypertrophy, inflammation of endothelial cells is observed and is associated with apoptosis of endothelial cells. Therefore, apoptosis of endothelial cells can trigger the initial event for progression of PAH. Vascular endothelial growth factor receptor blockade has been noted as a possible mechanism for endothelial cell apoptosis, followed by the selection of apoptosis-resistant clones, which lead to the formation of plexiform lesions with severe angio-obliterating lesions.[5)]

The article by Hong et al.[6)] suggests a role for bosentan in attenuating apoptosis and inflammation of endothelial cells. Their results indicate decreases in both caspase-3 and vascular endothelial growth factor in the bosentan-treated group. The proinflammatory cytokine, interleukin-6, was decreased and mRNA expressions of tumor necrosis factor (TNF)-α were decreased. Potential effects of bosentan to reduce apoptosis have been also reported in neuronal cells through the up-regulation of bcl-2 gene expression and decreased expression of the apoptotic protein, caspase.[7)] These observations suggest that bosentan may prevent disease progression in an early stage by preventing endothelial apoptosis and inflammatory response.

Another interesting suggestion is the expanding indication of bosentan to other diseases. Overexpression of endothelin-1 in mice resulted in a cardiomyopathy resembling doxorubicin-induced cardiomyopathy. Bien et al.[8)] reported that bosentan inhibits doxorubi-

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cin-induced cardiomyopathy in a mouse model. Pretreatment with bosentan resulted in reduction of TNF-α and Bax expression. Interestingly, ET antagonists are proapoptotic and antiproliferative in human colon cancer cells.[9]

Therefore, beyond its role as a vasodilator, bosentan has the potential to attenuate apoptotic cells, and this property can be applied to other disease associated with cell apoptosis.

References

1. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.
2. Galiè N, Rubin Lj, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093-100.
3. Rubin LJ. Endothelin receptor antagonists for the treatment of pulmonary artery hypertension. *Life Sci* 2012;91:517-21.
4. Sitbon O, Morrell N. Pathways in pulmonary arterial hypertension: the future is here. *Eur Respir Rev* 2012;21:321-7.
5. Malenfant S, Neyron AS, Paulin R, et al. Signal transduction in the development of pulmonary arterial hypertension. *Pulm Circ* 2013;3:278-93.
6. Hong YM, Kwon JH, Choi S, Kim KC. Apoptosis and inflammation associated gene expressions in monocrotaline-induced pulmonary hypertensive rats after bosentan treatment. *Korean Circ J* 2014;44:97-104.
7. Gong S, Peng L, Yan B, et al. Bosentan reduces neuronal apoptosis following spinal cord ischemic reperfusion injury. *Spinal Cord* 2013. [Epub ahead of print]
8. Bien S, Riad A, Ritter CA, et al. The endothelin receptor blocker bosentan inhibits doxorubicin-induced cardiomyopathy. *Cancer Res* 2007;67:10428-35.
9. Peduto Eberl L, Bovey R, Juillerat-Jeanneret L. Endothelin-receptor antagonists are proapoptotic and antiproliferative in human colon cancer cells. *Br J Cancer* 2003;88:788-95.

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