Bromodomain-Containing Protein 4: the Epigenetic Origin of the Cancer Paradigm in Pulmonary Arterial Hypertension

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Background: Pulmonary arterial hypertension (PAH) is associated with sustained DNA damage accounting for a PARP-1-dependent downregulation of miR-204. By an unknown mechanism, miR-204 downregulation promotes the expression of oncogenes implicated in PAH. Once activated, they contribute to the pro-proliferative and anti-apoptotic phenotype of PAH-pulmonary arterial smooth muscle cells (PAH-PASMC). In cancer, the increase of the epigenetic reader Bromodomain-containing protein 4 (BRD4) sustains cell proliferation. Interestingly, BRD4 is upregulated by DNA damage and is a predicted target of miR-204.

Hypothesis: We hypothesized that the PARP-1/miR-204-dependent upregulation of BRD4 triggers the oncogenes-dependent pro-proliferative and anti-apoptotic phenotype seen in PAH-PASMC.

Methods: Using human lung tissues and isolated PASMCs, we demonstrated that PAH-PASMC have increased BRD4 expression, which triggers the proliferation/apoptosis imbalance observed in PAH-PASMC. Rats with Sugen-induced PAH (SU5416 20mg/kg + Hypoxia) were treated with BRD4 siRNA nebulization (1 nmol/week for 2 weeks) after PAH establishment.

BRD4 is overexpressed in distal PAs and PASMCs of PAH patients

Deregulation of miR-204 triggers BRD4 expression

BRD4 inhibition downregulates oncogenes expression

BRD4 inhibition restores mitochondrial functions

Conclusion: BRD4 upregulation contributes to the proliferative and anti-apoptotic phenotype seen in PAH-PASMC, whereas BRD4 inhibition improves PAH. As BRD4 inhibitors have recently been developed and tested in cancer, this offers a short-term new therapeutic perspective for PAH patients.