The bromodomain-containing protein 4: the epigenetic origin of the oncogenic signature in pulmonary hypertension

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Background: As in cancer, 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 promotes the expression of several oncogenes implicated in PAH including Survivin, Bcl-2, Pim-1 and c-Myc. Once activated, by affecting the mitochondrial function through the transcription factor NFAT, they contribute to the pro-proliferative and anti-apoptotic phenotype of PAH-pulmonary arterial smooth muscle cells (PASMC). In cancer, studies demonstrated that the epigenetic reader Bromodomain-containing protein 4 (BRD4) increases transcription of multiple oncogenes sustaining 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 observed 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-PASMCs. Finally, rats with Sugen-induced PAH (SU5416 20mg/kg + Hypoxia) were treated with BRD4 siRNA nebulization (1 nmol every three days for 2 weeks i.t.) after PAH establishment. Rats underwent follow-up echocardiography and right heart catheterization before sacrifice.

Results:

**BRD4 is overexpressed in distal PAs and PASMCs of PAH patients**

Deregulation of PARP-1 /miR-204 axis triggers BRD4 expression

**BRD4 inhibition restores the proliferation/apoptosis balance**

**BRD4 regulates oncogene expression in PAH**

**BRD4 inhibition reverses established PAH in the Sugen/Hypoxia rat model**

Conclusion: Our study suggests an important role for BRD4 in pulmonary hypertension and opens the door to new avenues of investigation and proposes BRD4 as a putative treatment for PAH.