Implication of DNA Damage Signaling and Epigenetic Readers in Metabolic Disorder Observed in Vascular Wall of Ischemic Patients

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Background: Coronary artery disease (CAD) is the most common cause of heart attacks. Evidence demonstrated that coronary artery stenosis have increased inflammation leading to sustained DNA damage. In cancer, through the activation of poly(ADP)ribose-polymerase 1 (PARP-1), a critical enzyme acting as a DNA damage sensor, and the epigenetic reader Bromodomain-containing protein 4 (BRD4). DNA damage promotes mitochondrial/metabolic dysfunction contributing to cell proliferation.

Hypothesis: In light of these observations, we hypothesized that impaired mitochondrial/metabolism triggers DNA damage signaling in coronary artery stenosis leading to CoASMC proliferation and thus vessel narrowing.

Methods: Human coronary arteries were isolated after heart transplantation and coronary artery smooth muscle cells (CoASMC) were freshly isolated from patients with or without CAD. DNA damage was assessed using 53BP1 (immunohistochemistry) and γ-H2AX (immunofluorescence and western blot). PARP-1, BRD4 and PGC1-α expressions were measured by western blot. Mitochondrial (TMRM) and metabolic dysfunctions (Seahorse XF24) were compared between CoASMC isolated from CAD (stenosis) and non-CAD patients. Cells were treated with a PARP-1 (Veliparib 10µM) or a BRD4 (JQ1 1µM) inhibitor for 48 hours to assess their implication in the proliferation process (Ki67).

DNA damage and BRD4 expression are increased in remodeled coronary arteries

DNA damage and PARP-1 are increased in CoASMC isolated from remodeled coronary arteries

Mitochondrial and metabolic functions are disturbed in CoASMC from remodeled coronary arteries

CoASMC from remodeled arteries exhibit increased proliferation in a PARP-1/BRD4-dependent manner

Conclusion and Perspectives: Our study suggests an important role for BRD4 signaling and metabolic disorder in CAD and opens the door to new avenues of investigation and treatment. A carotid angioplasty rat model exhibits a phenotype similar to the one seen in CAD patients. Thus, a study to evaluate the therapeutic potential of BRD and PARP-1 inhibitors on vascular remodeling is ongoing.

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