Introduction

**SMARCB1** is one of the core subunits of the SWI/SNF complex, an ATP-dependent chromatin remodelling complex.

Malignancies are characterized by simple genomes and lack of somatic events, suggesting that the dysregulation of the SWI/SNF machinery is sufficient to drive highly malignant states [1].

Although SWI/SNF dysregulations are related to approximately 20% of human malignancies [2], lack of conditional genetic models of SMARCB1-deficient tumors has made it difficult to investigate the molecular bases and dependencies associated with SMARCB1 loss due to the embryonic lethality associated with SWI/SNF disruption.

Renal medullary carcinoma (RMC), an aggressive renal tumor that afflicts primarily young individuals of African descent with sickle cell trait [3]. RMC is also characterized by the complete loss of the SMARCB1 tumor suppressor [4], positioning it as an ideal tumor model for studying the role of SWI/SNF dysregulation in tumorigenesis.

We hypothesize that sickling red blood cells are promoting a hypoxic microenvironment in the renal medulla that is selecting for the loss of the tumor suppressor SMARCB1.

Results

**SMARCB1** devoid tumors are resistant to hypoxic conditions, while SMARCB1-proficient tumors are sensitive to hypoxic conditions. (a) Western blotting analysis of MCT1 cells co-overexpressing either SMARCB1wt or SMARCB1K62R constructs. MCT1 cells co-overexpressing either SMARCB1wt or SMARCB1K62R, and SMARCB1K62R grown in either normoxia or hypoxia. (b) CD6 was detected in 10% human kidney samples as shown above. Immunohistochemistry Images of hypoxia-inducible factor (HIF)-alpha antibody with SMARCB1wt, SMARCB1K62R, and SMARCB1K62R after prolonged exposure to normoxia and hypoxia. P-values were calculated with Student’s t-test in Prism GraphPad.

Future Direction

- Elucidate the E3 ubiquitin ligase involved in ubiquitinating SMARCB1.

- Investigate the role of the SWI/SNF complex in hypoxia response.

Conclusion

**SMARCB1** is degraded via ubiquitin-mediated proteasomal degradation pathway during extreme hypoxic stress.

SMARCB1-deficient kidney cells are resistant to hypoxia stress and maintain viability and growth compared to SMARCB1-proficient counterparts.

Impairing the degradation of SMARCB1 with lysine residue mutation K62 decreases cell viability and increases senescence under hypoxic stress, suggesting that SMARCB1-deficiency is selected for and required for survival under hypoxic stress.

Technique/Methods

1. **Renal ischemia is associated with chronic hypoxia in sickle cell trait mouse.** (a) Schematic of genetically engineered mouse model (GEMM) (b) 3D confocal reconstruction of renal epithelia (EPI) and FITC-dextran (GFP) in adult mice (n=4-5) with kidney-specific CDH50™ and conditional ROFL™ (c). Quantification of the diameter (d) and length (l) of the blood vessels (1 = white/atheroma, 3 = lobules) is possible. (d) H&E of mice kidney after injection with HypoxiPink (0). Quantification of the optical density of hemispheric periostum (HPP) staining for 30 images was done using ImageJ. Data are expressed as mean value ± SEM, with P-value calculated by student’s t test. (e) Immunofluorescence (IF) analysis of HypoxiPink (red) levels in wild-type mice (n=5) compared to sickle cell trait mice (n=3). Aquaporin 2 (AQP2, green) was used to localize renal medullary region.

2. **SMARCB1 regulates the hypoxic stress response in sickle cell trait during the pathogenesis of renal medullary carcinoma.**

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