Team 13 - Genetics and Metabolism of Rare Cancers

Loss of SDHB, but not SDHD, promotes dysregulated oxidative stress and vulnerability to ascorbate

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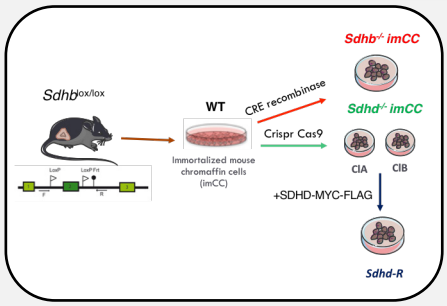
Background

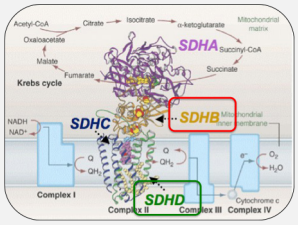
Pheochromocytomas and **Paragangliomas (PPGL)** are rare tumors of the sympathetic and parasympathetic nervous systems. They are **inherited in 40% of all cases** with **SDHx genes (SDHA, SDHB, SDHC and SDHD)** being the most frequently mutated. SDHA and SDHB encode the two catalytic subunits of succinate dehydrogenase (SDH), while SDHC and SDHD code for the anchoring subunits of the enzyme. Although mostly benign, PPGL may become **metastatic in around 15% of cases. SDHB mutations** are the first risk factor of PPGL metastatic evolution. It is estimated that **50% of SDHB** mutated patients are at risk of developing a **metastatic disease** while **96% of SDHD** mutation carriers will develop **benign tumors.**

In order to understand **the metastatic phenotype associated with SDHB loss,** we generated and characterized an *Sdhd-/-* chromaffin cell line and compared it to preexisting *Sdhb-/-* chromaffin cell line.

Generation of cell lines

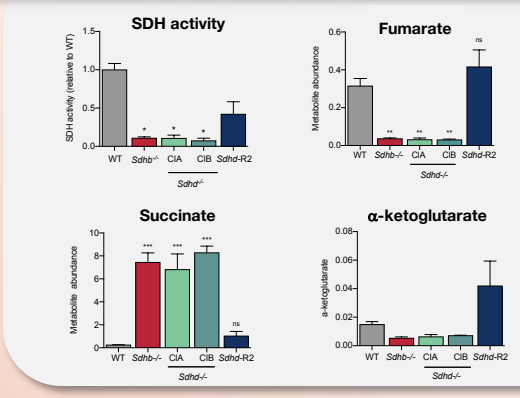


Letouzé et al., Cancer Cell. 2013

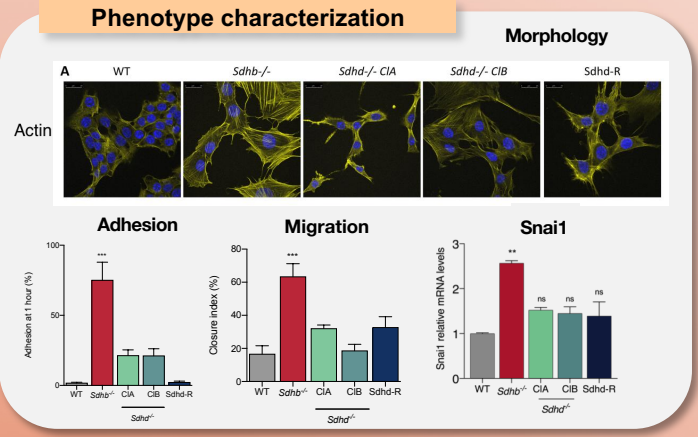


Hedersted L., Science 2003

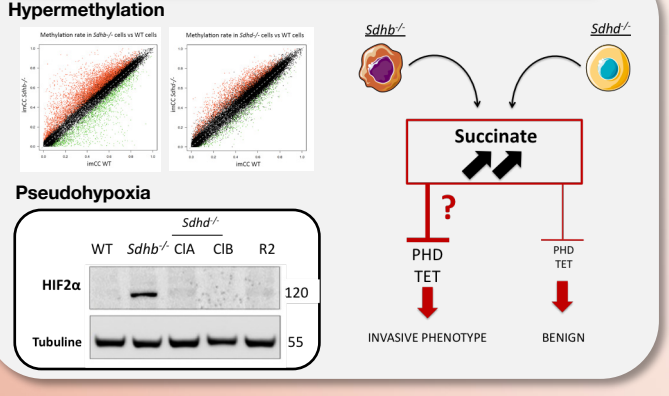
Validation of the *Sdhb* and *Sdhd* KO models



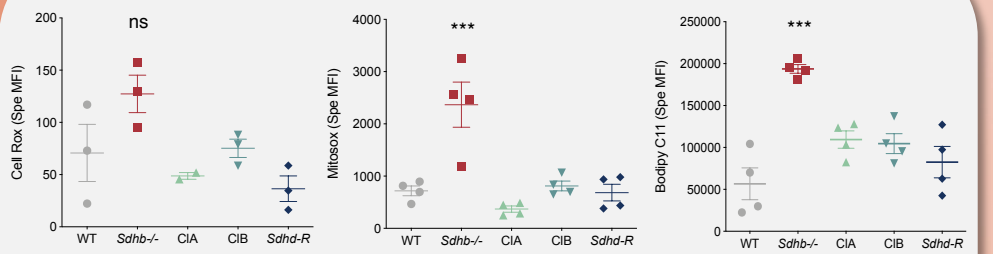
Phenotype characterization



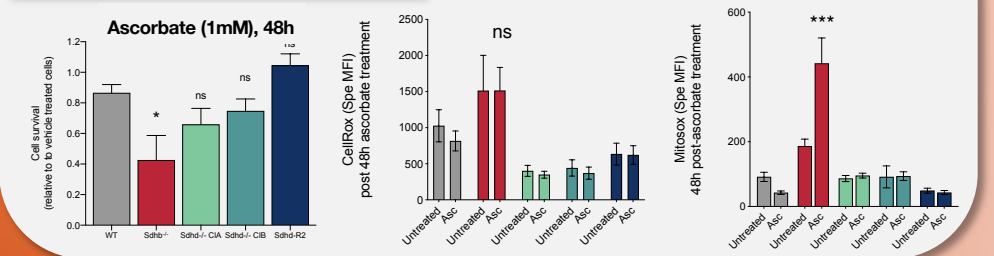
Hypermethylation and Pseudo-hypoxia



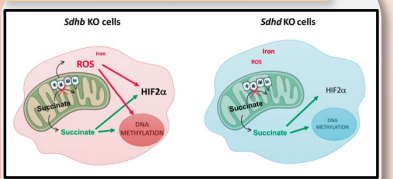
Oxidative stress



Ascorbate treatment



Conclusions



- In *Sdhb* KO cells, a combination of succinate accumulation and high ROS levels may account for the increased inhibition of TET and PHD hydroxylases.
- Ascorbate treatment appears as a promising prospect to treat patients with SDHB-dependent metastatic forms of PPGL.

Perspectives

Look further into the role of *ascorbate in vivo* in order to provide a treatment for metastatic forms of PPGL.