



## **A mitochondrial switch promotes tumor metastasis**

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### **Purpose:**

Cancers evolve a subpopulation of tumor cells that metabolically rely on glycolysis uncoupled from oxidative phosphorylation irrespectively of oxygen availability. Given that most metastases are abnormally avid for glucose (which is the rationale for their clinical detection using FDG-PET) and because clinical data show a positive correlation between lactate production and tumor metastasis, we reasoned that cells performing aerobic glycolysis could constitute a population of metastatic progenitor cells that would remain glycolytic in the blood stream.

**Experimental Design:** Darwinian selection was used to obtain superinvasive SiHa human cervix adenocarcinoma cells *in vitro* and supermetastatic B16-F10 mouse melanoma cells *in vivo*. Cell metabolism was analyzed using enzymatic assays and flux measurements. Data were confirmed using molecular biology approaches and mouse models of metastatic cancer.

### **Results:**

Our working hypothesis was that cancer cells performing aerobic glycolysis could constitute a population of metastatic progenitor cells. We found a different metabolic phenotype, though. Indeed, using serial rounds of *in vitro* selection of highly invasive tumor cells (starting from wild-type SiHa cells) and *in vivo* selection of supermetastatic tumor cells (starting from B16-F10 cells), we identified a mitochondrial switch corresponding to an overload of the TCA cycle with preserved mitochondrial functions (including ATP production) but increased mitochondrial superoxide production. The switch provided a metastatic advantage, which was phenocopied by moderate OXPHOS inhibition associated with mild mitochondrial superoxide increase. Thus, two different events, OXPHOS overload or moderate OXPHOS inhibition, promote superoxide-dependent tumor cell migration, invasion, clonogenicity, and metastasis; demonstrating the central role of mitochondrial superoxide generation in the pathogenesis of metastasis. Consequently, we report that mitochondria-specific superoxide scavenging (using mitoTEMPO or mitoQ) inhibits metastatic dissemination from primary mouse and human tumors, which opens a new avenue for the therapeutic prevention of tumor metastasis.

**Conclusion:** Mitochondrial superoxide promotes tumor metastasis and can be targeted therapeutically.

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