NORMAL HEMATOPOETIC STEM CELLS CAN EXHIBIT METABOLIC FLEXIBILITY SIMILAR TO CANCER CELLS

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Backgrounds :

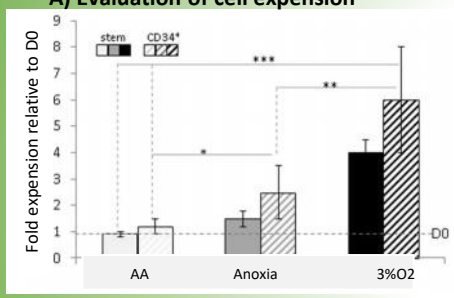
Cancer stem cells (CSC) possess characteristics associated with normal stem cells. Also cancer cells endowed with the largest stem cell potential responsible throughout the duration of the disease, survive under severe conditions such as anoxia and/or ischemia developed inside the tumour tissue partly by activated mitochondrial anaerobic respiration The aim of this study is to test the hypothesis that normal stem cells, unlike mature cells, can survive under extreme conditions thanks to cancer cell-like metabolic adaptations

Materiels and Methods :

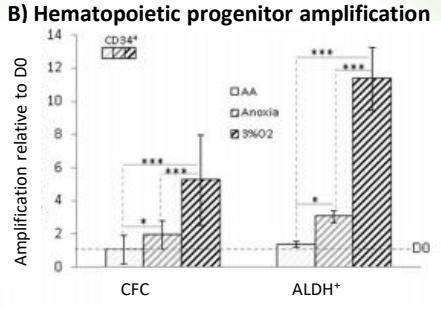
For this purpose we cultivated total CD34⁺ population englobing a majority of hematopoetic progenitors and rare stem cells, as well as selected CD34⁺CD38lowCD133⁺CD90⁺CD45RA population almost exclusively enriched in hematopoetic stem cells (HSC), under conditions of anoxia, anoxia/aglycemia ("ischemia-like") or under physiological conditions (3% O_2, "physioxia") for seven days prior to analysis.

Results 1 :

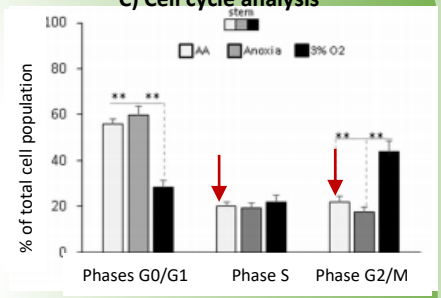
A) Evaluation of cell expension



B) Hematopoietic progenitor amplification



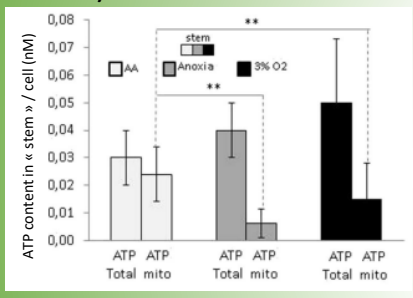
C) Cell cycle analysis



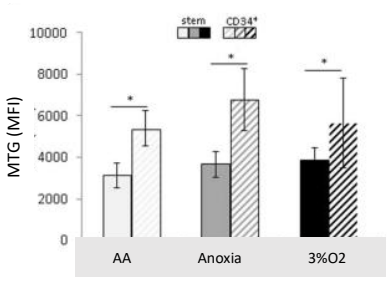
Results showed that despite a reduction in total cell fold expansion proportionate to the decrease in O_2 concentration (A), CD34+ cells, aldehyde dehydrogenase-expressing primitive cells (ALDH), and committed progenitors (CFC) expanded, even in anoxia. Interestingly, under ischemia-like conditions, stem and CD34⁺ cell populations are maintained at day-0 level (D0). Cell-cycle analysis revealed an accumulation of cells in the G0/G1 phase in anoxia or anoxia/aglycemia, with a fraction of cells (~40%) actively cycling (SG2M phases).

Results 2 :

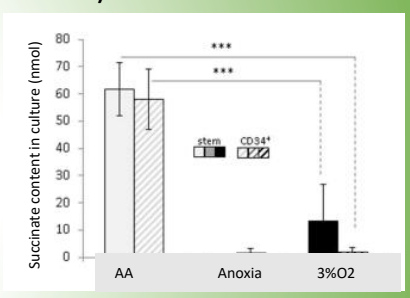
A) ATP level assessment



B) Mitochondrial mass



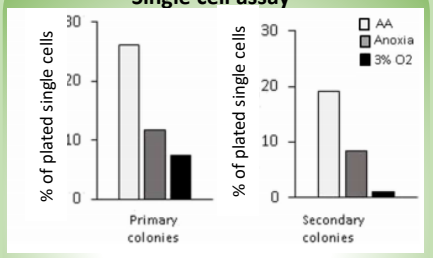
C) Succinate content



Bioenergetic analysis reveals that ATP profile (A), active mitochondrial content (B), and succinate accumulation (C) are indicative of anaerobic mitochondrial respiration in both HSCs and CD34⁺ progenitors under ischemia-like conditions.. In contrast, anoxic condition provokes complete glycolytic energetic orientation.

Results 3 :

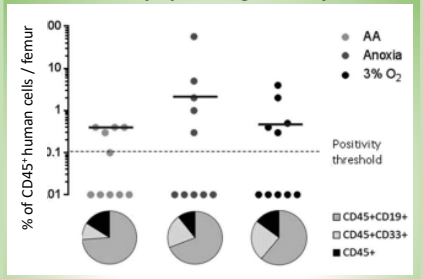
Single cell assay



A single cells assay (estimation of stemness *in vitro* at individual cell level) showed that the stem cells with highest proliferative replicating and multipotent capacity are enriched in ischemic-like conditions. The population enriched.

Results 4 :

SCID repopulating activity



Long-Term in vivo Hematopoietic Reconstitution upon transplantation in immunosuppressed mice, of the cell cultivated in anoxia and AA was equal to that found in physioxia.

Conclusion

We demonstrate here that primitive hematopoietic cells show similar metabolic flexibility to CSCs, allowing them to survive a lack of O_2 and O_2/glucose.

Our study reveals that this feature is not the consequence of malignant transformation, but an attribute of stemness.

This could be a suitable approach providing primitive cell selection for the cell therapy and engineering purposes.