Influence of intermittent hypoxia on the vascular and tumor cell compartments: implications for anti-cancer therapies.

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INTRODUCTION

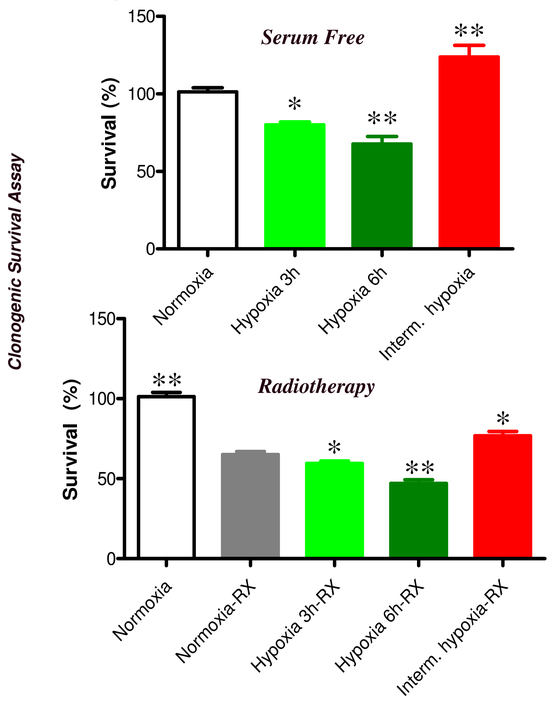
1. Hypoxia is a common feature in tumors associated with an increased resistance to anti-cancer therapies.
2. In addition to O_2 diffusion-limited hypoxia, another form of tumor hypoxia, named Intermittent Hypoxia (IH), is described:
IH is characterized by fluctuating changes in pO_2 due to heterogeneities in red blood cell flux within the tumor vascular network.
3. Peculiarities of IH are that tumor vasculature itself may be directly influenced by the hypoxic episodes and that re-oxygenation phases complicate the usual hypoxia-induced phenotypic pattern.

AIM OF THE STUDY

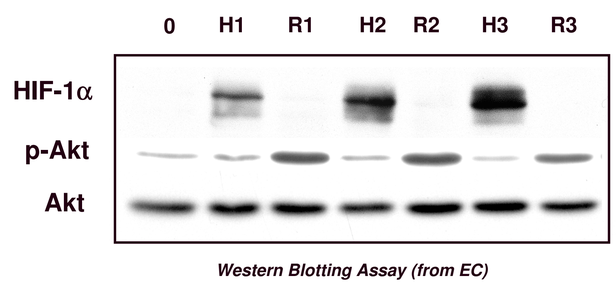
To examine whether IH may promote endothelial and tumor cell survival and thereby induce resistance to pro-apoptotic treatments.

RESULTS

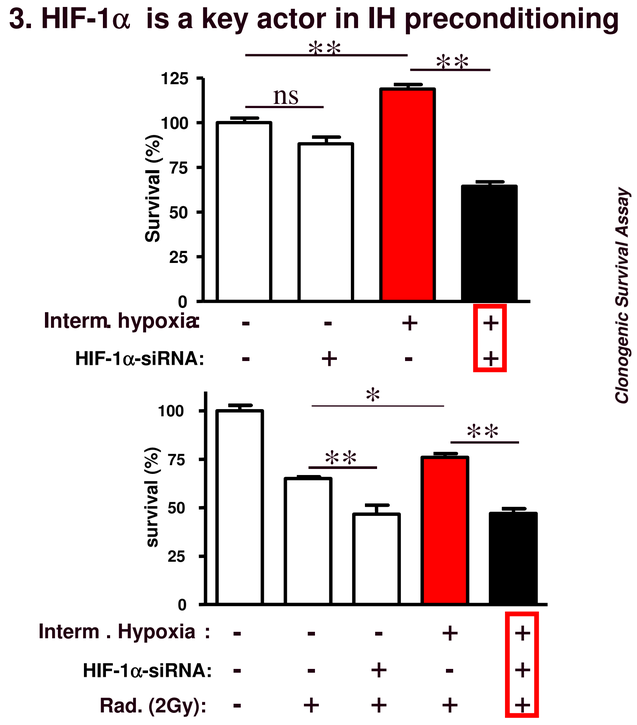
1. IH promotes EC survival



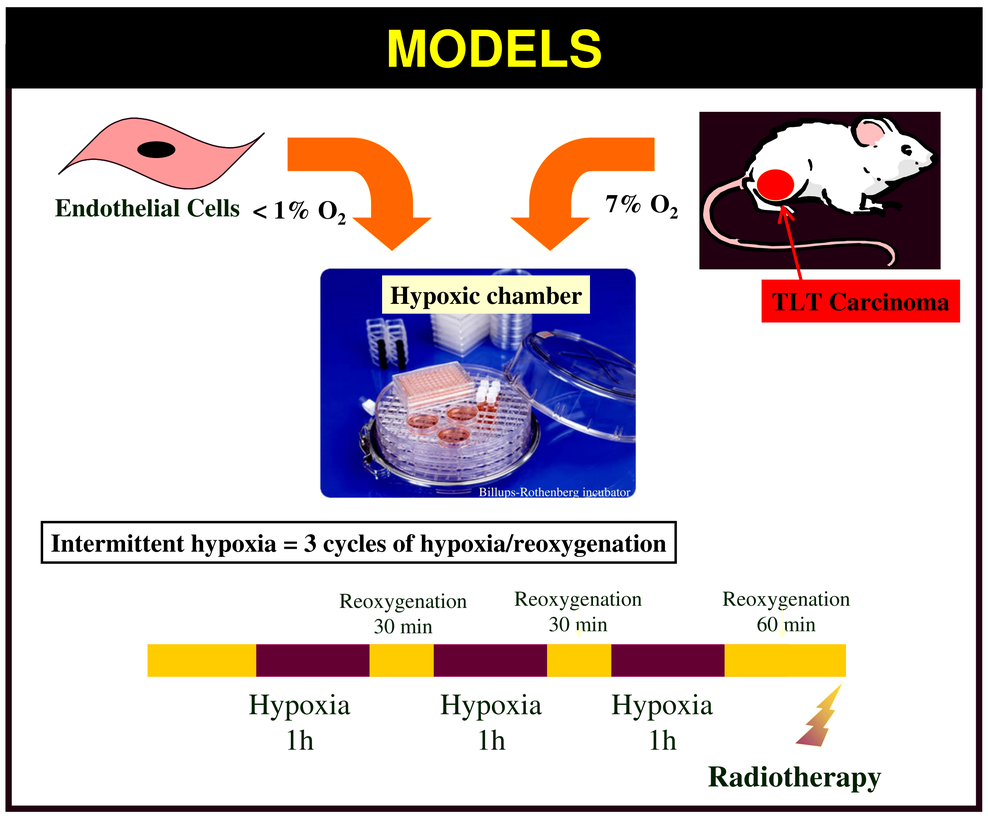
2. Activation of HIF-1α and Akt during Intermittent Hypoxia



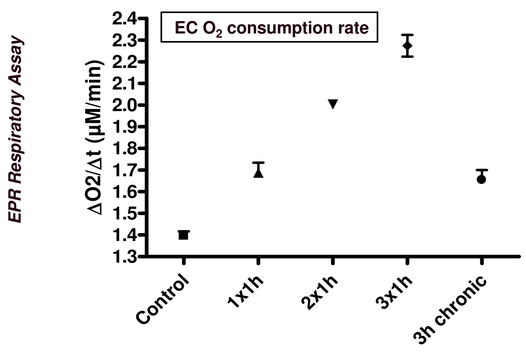
3. HIF-1α is a key actor in IH preconditioning

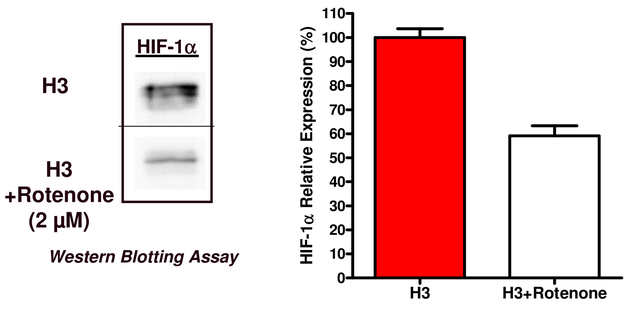


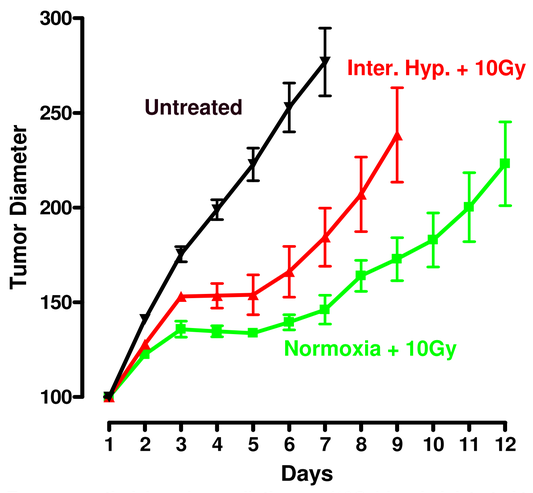
MODELS



4. IH stimulates the respiratory mitochondrial chain and is associated with HIF-1α stabilization

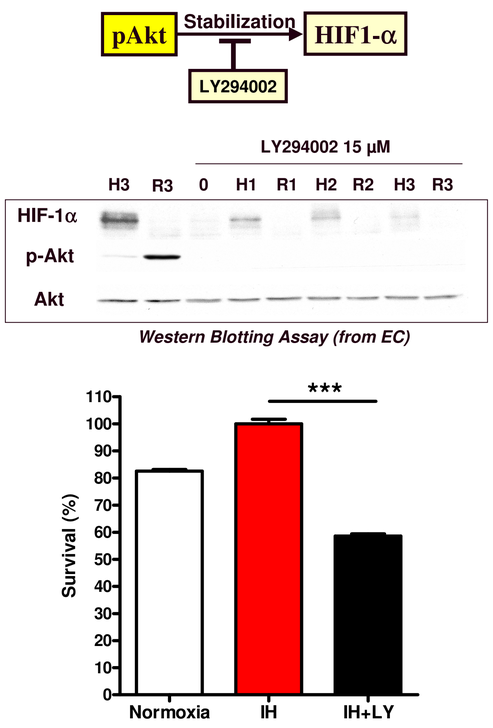






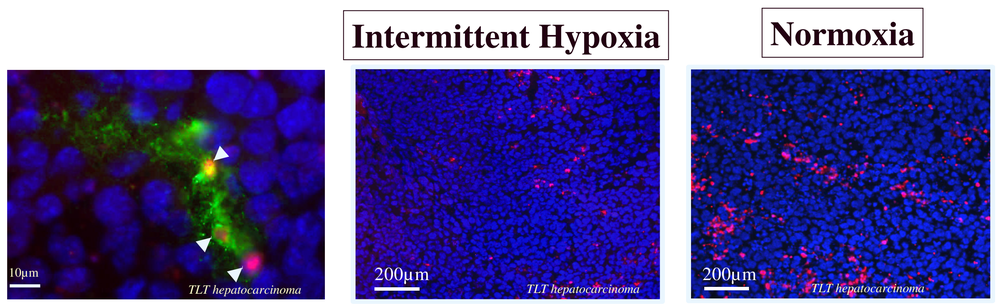
Tumor growth delay when radiotherapy (10Gy) is administrated to mice prechallenged by intermittent hypoxia (red) vs maintained in normoxia (green); p<0.01; and tumor growth in untreated mice (black).

5. Inhibition of HIF-1α reverses IH preconditioning

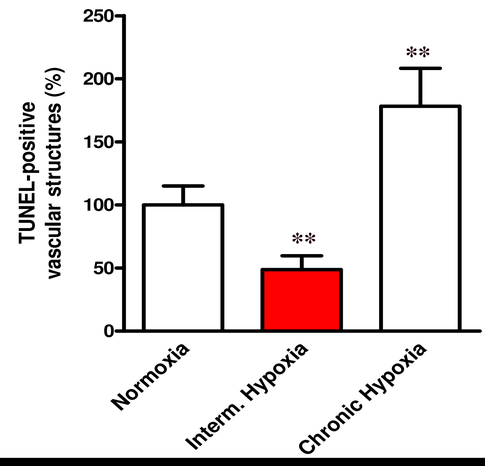


6. IH reduces the extent of apoptosis in both vascular and tumor cells *in vivo*

TLT liver tumor-bearing mice were exposed to either Intermittent Hypoxia (7%O_2), chronic hypoxia or ambient air and were locally irradiated.



Tunel-positive apoptotic nuclei (pink) within the CD31-immnostained (green) tumor vasculature or tumor section counterstained with DAPI (blue).



CONCLUSIONS

1. Intermittent hypoxia "preconditions" endothelial cells and tumor cells in such a way that they become more resistant to apoptosis (i.e. radiotherapy) and more prone to participate in tumor progression.
2. The stimulation of the mitochondrial respiration and the activation of the PI3K/Akt pathway during intermediary reoxygenation periods act as the major triggers of the stabilization of HIF-1α.
3. The accumulation of HIF-1α plays a key role in the IH preconditioning, underscoring the importance of drugs targeting HIF-1α to resensitize the tumor vasculature to anticancer treatments.

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