

Poster Abstract Submission

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Research Title 1	Chronic hypoxia is associated with transcriptomic reprogramming and increased genomic instability in cancer cells

Abstract:

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Abstract: Hypoxia afflicts the microenvironment of solid tumors fueling tumor malignancy. In this work we investigated the impact of long hypoxia exposure on transcriptional remodeling, tumor mutational burden (TMB), and genomic instability of cancer cells that were grouped based on their inherent sensitivity or resistance to hypoxia. To that end, a hypoxia score was used as a metric to distinguish between the most hypoxia-sensitive (hypoxia high (HH)), and most resistant (hypoxia low (HL)) cancer cells. These cells were subjected to chronic hypoxia (twenty passages at 1% oxygen) followed by whole exome sequencing and microarray analysis. We showed that the HH group was indeed more sensitive to hypoxia, showing significantly higher TMB ($p=0.03$) and copy number losses ($p=0.03$), as well as a trend of higher transcriptional response. Globally we found that cells adapted by decreasing expression of genes involved in metabolism, proliferation, and protein maturation, and increasing alternative splicing. They further accumulated mutations, in particular frameshift insertions, and harbored increased copy number alterations, indicating increased genomic instability. We could also validate the in vitro altered genes in patient data. Of interest, cells showing highest levels of TMB simultaneously experienced a significant downregulation of pathways involved in DNA replication and repair and chromosomal maintenance, suggesting that in chronic hypoxia these pathways are hijacked to drive genomic instability. Finally, we could put forth a common response to chronic hypoxia consisting of sixteen genes, including genes regulating angiogenesis, glycolysis, apoptosis, and proliferation. Our findings clearly show that chronic hypoxia could influence the adaptation of tumor cells, enabling their survival by promoting metabolic reprogramming, modulating proliferation, and increasing genomic instability. They additionally highlight key adaptive pathways that can potentially be targeted to prevent cancer cells residing in chronically hypoxic tumor areas from thriving.

Research Title 2	Targeting tumor hypoxia to increase efficiency of multimodal and immunological therapeutic strategies in pancreatic cancer
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Abstract:

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Abstract: The introduction of immunotherapy, in particular immune checkpoint inhibitors (ICI) that release the breaks on the immune response, has significantly improved outcomes in patients suffering from various types of cancer. However, pancreatic cancer remains the seventh cause of cancer-related deaths worldwide and this novel immunotherapeutic regimen seems to have limited effects. Therefore, novel therapeutic strategies targeting tumor microenvironment (TME) are mandatory to overcome the shortages of current immunotherapeutic concepts. Pancreatic ductal adenocarcinoma (PDAC) is characterized by a fibrous and hypovascularized TME resulting in oxygen-deprived tumor tissue with hypoxia-mediated effects such as increased malignant potential, modified immunity, and resistance to therapy. The presence of hypoxia deters response to ICI. Using a hypoxia gene signature, we have shown that PDAC patients with tumors that are highly hypoxic experienced significantly worse survival than patients with less hypoxic ones. The restoration of normoxia through anti-hypoxic treatment might prove a significant benefit for the response of such patients to ICI. Myo-inositol-trispyrophosphate (ITPP) is the first-of-its-class nontoxic agent that enhances oxygen release in hypoxia and synergizes with cytotoxic anti-cancer agents in preclinical-tumor models. So far, this reagent has not been tested in combination with ICI. This study aims at investigating ITPP in zebrafish patient avatars, which hold great potential as a quick screening tool to innovate patient treatment strategies. We will first validate the application of our signature as a hypoxia biomarker in human PDAC samples. We will investigate the ability of ITPP to restore normoxia with subsequent normalization of tumor vasculature and alleviate hypoxia in PDAC zebrafish xenografts and test the response of patient-derived xenografts to ITPP. Moreover, we will determine for the first time ITPP's efficacy in ameliorating response to ICI in PDAC mouse models. Results from this study could fuel clinical trials for ITPP and ICI combination therapy and could put forth a hypoxia biomarker that can aid in patient selection by predicting response to hypoxia-alleviating therapy, thus enhancing patient outcomes.