A therapeutic sphingosine 1-phosphate antibody increases tumor chemosensitivity by remodeling tumor vasculature. Prostate cancer as a model

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Background: The activation of HIF-1α has been identified as the master mechanism of adaptation to hypoxia. We identified the sphingosine kinase 1/sphingosine 1-phosphate (SphK1/S1P) pathway as a new modulator of HIF-1α activity under hypoxia in multiple cancer cell models (Ader et al, Cancer Res, 2008). S1P elicits proliferation, survival, angiogenesis, and is believed to exert most of its actions as a ligand for a family of specific GPCRs to elicit paracrine or autocrine signaling. We have suggested that inhibiting SphK1/S1P signaling, which is up-regulated under hypoxia, may help normalizing the tumor microenvironment and increase sensitivity to chemotherapy, in the broader concept of normalization of tumor vessels as tumor oxygenation is known to enhance response to chemotherapy (Ader et al., Cancer Res, 2009).

Methods: Quantitation of hypoxia, angiogenesis, tumor perfusion and treatment efficacy using an orthotopic (o.t) xenograft model of fluorescent HRPC cells.

Results: We provide in vitro evidence that inhibiting the S1P exogenous signaling, through pharmacological inhibition of its receptors or by taking advantage of a monoclonal antibody neutralizing S1P (sphingomab), blocks HIF-1α accumulation and its activity in prostate cancer cells under hypoxia. Second, using an o.t model of prostate cancer, we show that sphingomab inhibits intratumoral hypoxia, modifies vessel architecture and improves tumor perfusion within 5 days of treatment. Third, we demonstrate that an anti-S1P strategy sensitizes to docetaxel, the gold standard treatment for HRPC. A 5-day sphingomab pretreatment markedly sensitizes to docetaxel in an o.t. PC-3/GFP model established in nude mice. The combination sphingomab together with docetaxel was not only accompanied by a smaller primary tumor volume compared to docetaxel alone, but also significantly reduced the occurrence and number of metastases.

Conclusions: These data establish the proof-of-concept that blocking the exogenous action of S1P reduces intratumoral hypoxia and sensitizes to chemotherapy in prostate cancer animal model.

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