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HIF activation enhances FcγRIIb expression on mononuclear phagocytes impeding tumor targeting antibody immunotherapy

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Abstract:

Background: Hypoxia is a hallmark of the tumor microenvironment (TME) and in addition to altering metabolism in cancer cells, it transforms tumor-associated stromal cells. Within the tumor stromal cell compartment, tumor-associated macrophages (TAMs) provide potent pro-tumoral support. However, TAMs can also be harnessed to destroy tumor cells by monoclonal antibody (mAb) immunotherapy, through antibody dependent cellular phagocytosis (ADCP). This is mediated via antibody-binding activating Fc gamma receptors (FcγR) and impaired by the single inhibitory FcγR, FcγRIIb.
Methods: We applied a multi-OMIC approach coupled with in vitro functional assays and murine tumor models to assess the effects of hypoxia inducible factor (HIF) activation on mAb mediated depletion of human and murine cancer cells. For mechanistic assessments, siRNA-mediated gene silencing, Western blotting and chromatin immune precipitation were utilized to assess the impact of identified regulators on *FCGR2B* gene transcription.
Results: We report that TAMs are FcγRIIbbright relative to healthy tissue counterparts and under hypoxic conditions, mononuclear phagocytes markedly upregulate FcγRIIb. This enhanced FcγRIIb expression is transcriptionally driven through HIFs and Activator protein 1 (AP-1). Importantly, this phenotype reduces the ability of macrophages to eliminate anti-CD20 monoclonal antibody (mAb) opsonized human chronic lymphocytic leukemia cells in vitro and EL4 lymphoma cells in vivo in human FcγRIIb+/+ transgenic mice. Furthermore, post-HIF activation, mAb mediated blockade of FcγRIIb can partially restore phagocytic function in human monocytes.
Conclusion: Our findings provide a detailed molecular and cellular basis for hypoxia driven resistance to antitumor mAb immunotherapy, unveiling a hitherto unexplored aspect of the TME. These findings provide a mechanistic rationale for the modulation of FcγRIIb expression or its blockade as a promising strategy to enhance approved and novel mAb immunotherapies.

Keywords: Hypoxia, Hypoxia inducible factors, FcγRIIb, Fc gamma receptors, Tumor-associated macrophages, Monocytes, Monoclonal antibody, Tumor microenvironment, Resistance, Cancer