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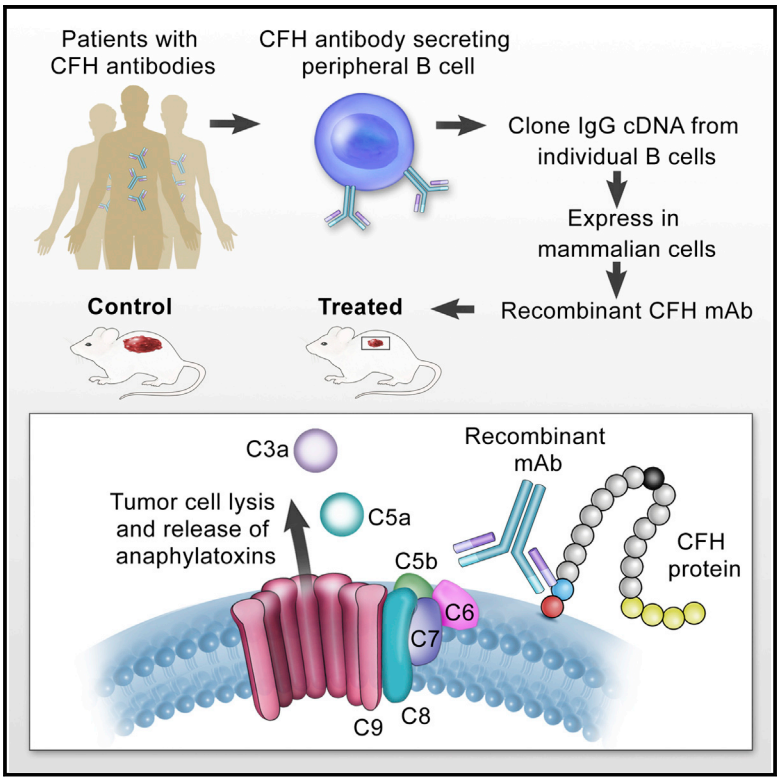
Cell Reports

A Therapeutic Antibody for Cancer, Derived from Single Human B Cells

Graphical Abstract



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In Brief

Bushey et al. clone antibodies against complement factor H (CFH) from single human B cells. CFH protects tumor cells from complement-dependent cytotoxicity (CDC). The authors demonstrate that a recombinant CFH antibody induces CDC of tumor cells, inhibits tumor growth in vivo, and stimulates infiltration of the tumor by lymphocytes.

Highlights

- Recombinant CFH mAbs were derived from B cells of patients with CFH autoantibodies
- Recombinant CFH mAbs promote tumor cell lysis and cause release of anaphylatoxins
- Recombinant murine CFH mAbs inhibit tumor growth in mice

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A Therapeutic Antibody for Cancer, Derived from Single Human B Cells

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SUMMARY

Some patients with cancer never develop metastasis, and their host response might provide cues for innovative treatment strategies. We previously reported an association between autoantibodies against complement factor H (CFH) and early-stage lung cancer. CFH prevents complement-mediated cytotoxicity (CDC) by inhibiting formation of cell-lytic membrane attack complexes on self-surfaces. In an effort to translate these findings into a biologic therapy for cancer, we isolated and expressed DNA sequences encoding high-affinity human CFH antibodies directly from single, sorted B cells obtained from patients with the antibody. The co-crystal structure of a CFH antibody-target complex shows a conformational change in the target relative to the native structure. This recombinant CFH antibody causes complement activation and release of anaphylatoxins, promotes CDC of tumor cell lines, and inhibits tumor growth in vivo. The isolation of anti-tumor antibodies derived from single human B cells represents an alternative paradigm in antibody drug discovery.

INTRODUCTION

Metastatic disease is responsible for the majority of cancer deaths, and unfortunately, many current drugs only offer modest benefits in progression-free survival. We have been studying the immune response in a distinct group of patients with early-stage disease who do not develop metastasis as an approach to developing therapeutic strategies (Amornsiripanitch et al., 2010). Our goal was to identify tumor-specific antibodies capable of initiating tumor cell death while stimulating a durable, long-term adaptive immune response. We previously reported an association of autoantibodies to a complement regulatory protein, complement factor H (CFH), with early-stage non-small cell lung cancer (NSCLC) and found that patients with stage I NSCLC had a significantly higher incidence of anti-CFH antibody than those with late-stage NSCLC ($p = 0.0051$). This association led to the hypothesis that CFH antibodies that arise in lung cancer patients may promote anti-tumor cell activity and that CFH antibody administration might provide a unique way to stimulate a long-term immune response and treat cancer. We set out to isolate and characterize human CFH antibodies starting from the memory B cells of patients with the autoantibody in an effort to develop a therapy that would recapitulate the native immune response.

CFH is a regulatory protein that protects host cells from attack and destruction by the complement system by inhibiting the alternative pathway of complement-mediated lysis (Ferreira et al., 2010; Makou et al., 2013). CFH prevents the deposition of complement C3b on the cell surface by several mechanisms. Deposition of C3b initiates the formation of cell-lytic membrane attack complexes (MACs) leading to cell lysis. Thus, CFH inhibition of the deposition of C3b on the cell surface protects against cell lysis. Tumor cells take advantage of the protection conferred by CFH in order to evade destruction by the complement system (Ajona et al., 2007; Junnikkala et al., 2000; Varsano et al., 1998; Wilczek et al., 2008). We hypothesize that by neutralizing this protective protein, patient antibodies to CFH allow complement activation and tumor cell lysis, resulting in the release of anaphylatoxins and modulation of the adaptive immune response, thus suppressing tumor growth while forestalling metastasis.

In order to develop a CFH antibody as a cancer therapeutic, targeting the same epitope that is recognized by the autoantibodies of cancer patients would be essential to prevent off-target effects, since CFH is a ubiquitous protein that binds to the surface of host cells. CFH is a multifunctional 150 kDa protein