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Monoclonal antibodies targeting cell surface deposited complement fragment C3d potentiate cancer immunotherapy and eliminate antigen loss variants

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Treatment-induced loss of targeted cell surface antigens through trogocytosis or internalization reduces efficacy of monoclonal antibody (mAb) therapy of cancer. However, cells that escape therapy mediated by complement-fixing mAbs carry covalently deposited complement activation fragments on their cell surfaces, in particular C3d. We hypothesized that cell-associated C3d constitutes a neoantigen that could be exploited to selectively retarget cells escaping from therapeutic mAbs. We generated an anti-C3d IgG1 human/mouse chimeric mAb specific for human C3d that is not competed by full-length C3 in human serum.

We then set out to provide proof for the concept that complement-targeting mAbs can retarget cancer cells that survive mAb therapy. For this purpose, we used cells from chronic lymphocytic leukemia (CLL) patients that had substantially reduced CD20 levels due to *in vivo* treatment with the anti-CD20 mAb ofatumumab (OFA). The chimeric anti-C3d mAb bound cell surface C3d on these CLL cells *ex vivo* (K_D = 6.7nM), and mediated complement-dependent, and antibody-dependent cellular cytotoxicity and phagocytosis *in vitro*. CLL cells opsonized by C3d *in vivo* and reacted with the anti-C3d mAb *in vitro* were further C3d opsonized, resulting in an amplification that enhanced anti-C3d mAb binding capacity and killing of target cells.

In vivo, the anti-C3d mAb was effective in reducing tumor growth and extending survival in a mantle cell lymphoma xenograft mouse model. This complement-targeting mAb also depleted human primary CLL cells in the blood and spleens of xenografted NSG mice. Our results identify anti-C3d mAbs as a means to circumvent antigen loss by specifically and potently augmenting the therapeutic efficacy of complement-fixing mAbs.

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