Author’s response to reviews

Title: Two mechanisms of the enhanced antibody-dependent cellular cytotoxicity (ADCC) efficacy of non-fucosylated therapeutic antibodies in human blood

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Melissa Norton, MD
Editor-in-Chief, BMC Cancer

Dear Dr. Melissa Norton:

I herewith submit a manuscript titled “Two mechanisms of the enhanced antibody-dependent cellular cytotoxicity (ADCC) efficacy of non-fucosylated therapeutic antibodies in human blood” for the publication in BMC Cancer.

ADCC has recently been identified as one of the critical mechanisms of the clinical efficacy of therapeutic antibodies, especially anticancer antibodies (Cartron G et al. Blood 99: 754, 2002, Gennari R et al. Clin Cancer Res 10: 5650, 2004). However, ADCC of currently licensed therapeutic antibodies, in which the oligosaccharides attached to the Fc are fucosylated, is strongly inhibited by human plasma IgG through competition for binding of the therapeutics to FcγR on effector cells (Preithner S. et al. Mol Immunol 43: 1183, 2006), which causes such a high dose requirement in antibody therapies to keep the effective serum concentration over 10 µg/mL (Baselga J et al. Ann Oncol 12: 35, 2001, Berinstein NL et al. Ann Oncol 9: 995, 1998). On the other hand, therapeutic antibodies fully lacking the core fucose of the Fc oligosaccharides have been found to exhibit strong ADCC at lower concentrations with much higher efficacy than their fucosylated counterparts in humans ex vivo (Iida S et al. Clin Cancer Res 12: 2879, 2006).

In this manuscript, we assessed in detail the reasons why non-fucosylated antibodies are so effective in human blood, focusing on the actual binding of the
therapeutic agents both to antigens on target cells and to FcγR on effector cells in individual human blood. Using human ex vivo B-cell depletion assay with anti-CD20 IgG1 rituximab, the binding of the therapeutic agents both to antigens on target cells and to FcγR on effector cells were analyzed comparing the intensity of ADCC in human blood. Non-fucosylated anti-CD20 showed sufficiently high FcγRIIIa-binding activity to overcome competition with plasma IgG for binding to FcγRIIIa on natural killer (NK) cells while the binding of fucosylated anti-CD20 to FcγRIIIa was almost abolished in the presence of human plasma and failed to recruit NK cells effectively. Although the individual serum IgG from 12 donors displayed slight differences in the IgG1 concentration and the relative amount of non-fucosylated Fc oligosaccharides, we did not detect a significant difference in the serum inhibitory effect on the ADCC induced by fucosylated anti-CD20 in individuals. Moreover, the enhanced ADCC of non-fucosylated anti-CD20 was inhibited by fucosylated forms of anti-CD20 through competition for binding to antigens on target B cells. These results demonstrated that removal of fucosylated antibody ingredients from antibody therapeutics elicits high ADCC in human blood by two mechanisms: namely, by evading the inhibitory effects both of plasma IgG on FcγRIIIa binding (effector side interaction) and fucosylated antibodies on antigen binding (target side interaction).

The manuscript has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. Acknowledgment that all authors have contributed significantly, and that all authors are in agreement with the content of the manuscript.

We would be grateful if the manuscript could be reviewed and considered for publication in BMC Cancer.

We hope to hear from you soon.

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