HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2020 October 01.

Published in final edited form as:

Clin Cancer Res. 2020 April 01; 26(7): 1773. doi:10.1158/1078-0432.CCR-19-3935.

Innate and Acquired Resistance to Anti-EGFR Therapy—Letter

Janardan P. Pandey

Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, South Carolina, USA

I read with great interest the recent article by Parseghian and colleagues (1), presenting a review of the mechanisms underlying the innate and acquired resistance to anti-EGFR therapy. This "in-depth review" of the resistance mechanisms, however, does not include the possible host antibody responses to the immunogenic epitopes present on the therapeutic anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab (2). Both cetuximab and panitumumab express GM (γ marker) allotypes that are highly immunogenic in subjects lacking these determinants. For instance, GM 3 allotype is expressed in the CH1 region of cetuximab (3). Subjects lacking GM 3 could have pre-existing anti-GM 3 antibodies because of maternal-fetal incompatibility (4). The administered cetuximab and the pre-existing anti-GM 3 antibodies would form immune complexes that would be removed from the system by phagocytic cells, leading to *de novo* resistance to cetuximab therapy. Repeated infusion of cetuximab could also generate anti-GM 3 antibodies, leading to acquired resistance to this immunotherapy.

Similar resistance mechanisms could also be envisioned for panitumumab therapy. In summary, effective "personalized immunotherapeutic approaches" must take into account the immunogenicity of GM allotypes expressed on the therapeutic antibodies.

Acknowledgments

The author's laboratory is currently supported by grants from the National Institutes of Health and the Cystic Fibrosis Foundation.

References

1. Parseghian CM, Napolitano S, Loree JM, Kopetz S. Mechanisms of innate and acquired resistance to anti-EGFR therapy: A review of current knowledge with a focus on rechallenge therapies. Clin Cancer Res 2019; 25:6899–908. [PubMed: 31263029]
2. Pandey JP. Mechanism of resistance to cetuximab therapy in colorectal cancer: Possible role of antibodies to immunoglobulin allotypes. MAbs 2012; 4:553–4. [PubMed: 22820100]
3. Ternant D, Arnoult C, Pugnière M, Dhommée C, Drocourt D, Perouzel E, et al. IgG1 allotypes influence the pharmacokinetics of therapeutic monoclonal antibodies through FcRn binding. J Immunol 2016; 196:607–613. [PubMed: 26685205]
4. Fudenberg HH, Fudenberg BR. Antibody to hereditary human gamma-globulin (Gm) factor resulting from maternal-fetal incompatibility. Science 1964; 145:170–171. [PubMed: 14171557]

Correspondence: Dr. Janardan P. Pandey, Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, South Carolina, SC 29425 (pandeyj@musc.edu), Tel: 843-792-4360, Fax: 843-792-4882. .

The author has no conflict of interest.