Diversification of IgA antibody specificities by mild chemical modification?

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Intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) consisting mainly of IgG antibodies are used for substitution therapy in humoral immunodeficiency or as a high-dose treatment for inflammatory and autoimmune conditions. The antibodies in these preparations are derived from thousands of blood donors and collectively represent the donors' IgG repertoires, which in humans is both public and private [1,2]. Mild chemical modification of antibodies has been proposed as one of several strategies to improve the efficacy of polyclonal immunoglobulin preparations [3], as this approach can lead to further diversification of antibody specificities beyond somatic recombination, junctional diversity and somatic hypermutation [4]. Indeed, mild chemical modification of IVIG has shown to improve survival in experimental models of sepsis and aseptic systemic inflammatory response syndromes [5], and to enhance pro-apoptotic effects on leukocytes under inflammatory conditions [6].

While IVIG and SCIG preparations mainly consist of IgG antibodies, evidence suggests that IgA formulations might also be beneficial for clinical applications and exhibit idiosyncratic advantages [3,7]. The heavily N-glycosylated secretory component (SC) that stabilizes IgA also prevents rapid proteolysis of IgA dimers and multimers in the hostile environment of the digestive tract. Therefore, the oral route might one day be used for passive digestive transfer of specific or polyclonal IgA that could be very beneficial to IgA-deficient patients that presently do not benefit from any specific treatment [8]. Any technical clue, as the one tested by Gorshkova et al. in this issue of *Pharmacology* [9], to further diversify anti-microbiota reactivity of future therapeutic IgA preparations, would therefore be more than welcome. Indeed, IgA polyreactivity appears to represent a key biological feature of this antibody,

eventually accounting for its ability to regulate immune/microbiota homeostasis [8,10].

Gorshkova et al. report that protein-modifying agents can alter the repertoire of secretory IgA and that exposure to acidic pH broadens the range of reactivities to common and distinct pathogens [9]. Specifically, low pH treatment of colostrum and breast milk IgA broadened the recognition of bacterial antigens from *E. coli* and *S. aureus*, but also Colo205 cell antigens, and increased IgA binding to viral antigens from hepatitis C or D virus, human immunodeficiency virus type 2 and norovirus. However, the recognition of select bacterial antigens was also lost by low pH treatment. It remains unclear whether low pH treatment might partially denature some IgA, potentially leading to non-specific interactions. Conversely, it is also possible that bound materials that might co-purify with antibodies are removed by acid treatment, thereby offering more options for specific interactions. As opposed to low pH, treatment with ferrous ions had little or no effect on IgA binding to these antigens, while heme exposure increased reactivities of colostrum, but not breast milk, secretory IgA. Components of milk might affect the integrity of antibodies or block antibody reactivities, eventually requiring material processing prior to analysis [11], such as casein depletion by sodium phosphates employed in the study by Gorshkova. However, the divergent effect of modifying treatment on colostrum and milk IgA by heme, highlights the potential importance of co-factors that might directly influence IgA reactivities or effects of mild protein-modifying agents on antibodies in a biological context.

Microarray technology allows for the high-throughput analysis of antibody immunosignatures [1,2,12], and has been used to analyse reactivity profiles of IgA [13,14]. Gorshkova et al. tested native or modified secretory IgA against an array of

4’345 linear B cell epitopes, and while decreased or increased binding patterns were observed upon modification by different agents, treatment with acidic pH enhanced the polyspecificity of IgA in particular for common pathogens [9]. It is therefore tempting to speculate from the results of Gorshkova al. that mere gastric exposure of IgA preparations might improve their efficacy. Further in vivo studies will now be needed to document how such modified IgA preparations might impact functional microbial fitness and host-microbial mutualism [14], in any sort of way. However, it is clear that that the report of Gorshkova and colleagues in this issue of *Pharmacology* is an important first step.

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DISCLOSURES

The authors have no conflicts of interest to declare.

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FIGURE LEGEND

Fig. 1. Proposed concept of enhanced reactivities of IgA under mild protein-modifying conditions. Exposure to low pH enhances the range of viral epitopes recognized by secretory IgA.