Sialylated autoantibodies involved in disease activity of rheumatoid arthritis

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Sialylation, which is the process of adding sialic acid (SA) covalently to the terminal end of glycoproteins or glycans, plays a critical biological role not only in the maintenance of normal physiology but also in the participation to many pathological dysfunctions.[1–5] Sialylation modulating the targets influences the solubility, activity, and biological fate and is subsequently involved in the interaction with the microenvironment or cells.[1–5] Sialy medicine has become a more attractive study field in the host and environment. In addition, altered sialylation of the immune system is involved in various kinds of diseases, such as autoimmune diseases, cancer, or infectious diseases.[6–8] We are happy to learn an article studying the relationship between sialylation and autoimmune diseases, which has been published in the last December issue of the *Journal of the Chinese Medical Association*.[9] The authors conducted a translational medicine study to investigate the role of α2,6 SA levels of antibodies (Abs, including immunoglobulin G [IgG] or IgM against rheumatoid factor and anticyclic citrullinated peptide) on the disease activity of rheumatoid arthritis (RA).[9] Both animal model (collagen-induced arthritis [CIA] mice) and humans beings with RA were tested, and the results showed that a proportion of α2,6 SA-linked conserved *N*-glycans of IgG in total IgG was dramatically different from the disease mice to control mice and this difference was also apparent between patients with and without flare-up of RA.[9] CIA mice with arthritis attacks had a decreased ratio of α2,6 SA-linked IgG and total IgG than CIA induced mice without arthritis or normal control mice did.[9] The similar finding was also found in the clinical patients, because the ratio of α2,6 SA-linked IgG and total IgG was negatively correlated with clinical disease activity score in patients with RA,[9] hinting us that the higher ratio of α2,6-sialylated IgG/total IgG was a good indicator for patients without flare-up of RA and also suggesting that an increased α2,6-sialylated IgG may have a protective role in patients with RA.

However, the role of α2,6-sialylated IgM was not clear, because the ratio of α2,6 SA-linked conserved *N*-glycans of IgM/total IgM seemed be inconsistent. In mice, no statistically significant difference of the ratio of α2,6 SA-linked IgM/total IgM was identified among the CIA mice, non-CIA mice, and control mice.[9] By contrast, in patients with RA, the ratio of α2,6-sialyated IgM/total IgM was positively correlated with severity of RA,[9] hinting the higher level of α2,6-sialylated IgM is associated with more severity of RA and also suggesting that an increased α2,6-sialylated IgM may contribute to the flare-up of RA. Although the data seemed to be conflicted, it still confirmed the important role of sialylation in the modulation of immune response. The following is our comments.

First, without a template, cell-specific "programming" of homogenous target glycosylation is not possible although there are significant trends within the heterogeneity of the glycome are observed as function of diseases and microenvironment.[10] In addition, the immune response is a complex process, not only involved in the immune cells themselves but also their products, such as Abs, cytokines and growth factors. For example, our previous studies have shown that immune cells (natural killer [NK] cells) with changing sialylation will affect migration of NK cells and influence the ability of phagocytosis.[11,12]

Second, to obtain the markedly variable functions of Abs, 2 modifications to the constant domain control their activities are needed.[13] One is the irreversible genomic selection of isotype/subclass and the other is alterations in glycosylation.[13] Altered glycosylation, compared with irreversible genomic selection, may play a more critical role to modulate the immune system and to tune a broad range of biological activities.[13] In fact, the targeted site of the α2,6 sialylation of Ig is located at asparagine 297 (Asn297) of each heavy chain, which serves as a functional switch.[14] It is well known that sialylated IgG imposes a net inhibitory effect on the immune response.[10] Intravenous Ig (IVIg), used to treat the flare-up of RA or other inflammatory conditions, has an anti-inflammatory effect driven by a population of Abs bearing α2,6 sialylation.[13] Although IVIg is frequently applied in clinical practice, the precise mechanisms remains unclear.[13] There are 2 models proposed to explain the anti-inflammatory effect of IVIg.[13] One is that sialylation constrains the Fc region (constant/crystallizable region) to a closed conformation and reduces Ab affinity.[13] The other is that sialylation is involved in other receptors,

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 123-124.

Received December 5, 2020; accepted December 5, 2020.

doi: 10.1097/JCMA.0000000000000480.

such as Siglect (SA-binding Ig-type lectins)/CD22 (cluster of differentiation-22), the C-type lectin dendritic cell immune-receptor, and the Fc receptor-like protein 5 that may bind sialylated structures to drive anti-inflammatory responses.[13]

Third, 4 IgG subclasses (IgG1, IgG2, IgG3, and IgG4) and 36 possible antibody glycans are identified, allowing up to 144 potential Fc regions for different functional states.[13] Among these, IgG1 is broadly used, based on their strong effector functions through binding of their Fc to proteins of the lytic complement pathway and cross-linking of $Fc_{\gamma}Rs$ widely expressed on many innate immune cells, such as NK cells, monocytes, macrophages, and neutrophils.[15] The $Fc_{\gamma}Rs$ include the activating receptors $Fc_{\gamma}R1$, $Fc_{\gamma}RIIA$, $Fc_{\gamma}RIIC$, $Fc_{\gamma}RIIIA$, and $Fc_{\gamma}RIIIB$, and the inhibitory receptor $Fc_{\gamma}RIIB$.[15] The current study by Drs. Liou and Huang limited to study total IgG may be inadequate to open the secret of Pandora's box (the role of sialylation of Ig), partly because sialylation is tightly regulated by numerous sialyltransferases (STs) and sialidases (neuroaminidases [NEUs]), and partly because different sugars and their related complex structure exist.[5] In 2019, the same group has investigated the relationship between the expression of certain types of STs and NEUs of monocytes and disease activity in patients with RA.[7] There are 4 targeted enzymes tested, including α2,3-ST1 (ST3Gal1), α2,6-ST1 (ST6Gal1), NEU1, and NEU3.[7] The authors suggested the important role of α2,3-sialylation but not α2,6-sialylation in disease activity of RA, because they found monocyte ST3Gal1 and NEU3 levels were correlated longitudinally with severity of RA.[7] By contrast, the relationship between the ST6Gal1 and severity of RA seemed to be not significant.[7] If ST6Gal1 plays an essential role for α2,6 sialylation,[1,3] it is wondering to know why the expression of ST6Gal1 in monocytes was not correlated with severity of RA,[7] but the 2020 article favored the protective role of α2,6-sialylated IgG in patients with RA.[9]

Fourth, glycosylation of Abs is a complex process involved in the addition and removal of the variably added sugars (SA, galactose, fucose, mannose, and others), which has been linked to altered Ab functionality.[13] For example, aglycosylated monoAbs, produced in *Escherichia coli* or mutated at Asn297 (Asn297A or Asn297G), lack effector function (Ab-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity), whereas the absence of fucose residues on the Fc glycan moiety is associated with augmented affinity for $Fc_{\gamma}RIIIA$.[15] Agalactosylation Abs arise before symptoms of RA and are considered as a diagnostic value for the patients with RA.[13] In fact, these autoimmune diseases might be associated with alternations in circulating Abs, which are not only in the quantity level but also in the quality level. Therefore, to provide a critical insight into novel Fc profiles that drive Ab function might need the fully understanding of the landscape of subclass and glycosylation change of Ig.[13]

Finally, we found that the research articles focusing on the translational medicine may provide us much information, which can be reproducible and repeated for testing, because the study translating from the bench works to the clinical works is not easy. We congratulate the successful publication of Drs. Liou and Huang and also appreciate their great contribution to the glycomedicine, as this field is still underdeveloped.

ACKNOWLEDGMENTS

This article was supported by grants from the Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 109-2314-B-075B-014-MY2 and MOST 109-2314-B-075-056), and Taipei Veterans General Hospital (V110C-082 and VGH109E-005-5).

The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

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