Aberrant sialylation of immune cells in rheumatoid arthritis

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Sialylation, or the covalent addition of sialic acid (SA) to the terminal end of glycoproteins, is a biologically important modification that is involved in the physiological function and pathological dysfunction, including embryonic development, reprogramming, oncogenesis, and immune responses, which is a tightly regulated cell- and microenvironment-specific process and orchestrated by numerous sialyltransferases (ST) and sialidases (neuraminidases [NEUs]).[1–5] Besides cancer and infection fields,[1,6–8] recent studies focused on the immune system on various kinds of diseases, such as autoimmune diseases.[9] We are happy to learn about Drs. Liou and Jang's article that has been published in the March issue of the *Journal of the Chinese Medical Association* to investigate the association of monocyte α-2,3-ST 1 (ST3Gal-1), NEU-3, α-2,6-ST 1 (ST6Gal-1), and NEU-1 levels with disease activity score 28 (DAS28) in human rheumatoid arthritis (RA).[10] The hypothesis was based on the observation that mouse monocytes' SA levels relate to their phagocytosis and immunoglobulin binding ability.[10] The authors enrolled 157 and 115 patients with RA and systemic lupus erythematosus (SLE), respectively, and 47 normal controls were used as the reference.[10] The results showed that disease activity of RA patients was correlated with monocyte ST3Gal-1 and NEU-3 levels, regardless of which analysis method or time point was performed, suggesting that monocyte ST3Gal-I and NEU-3 levels may be useful in monitoring the disease activity of RA patients.[10] We congratulate the success of publication from the authors, and the current study is interesting and worthy of discussion.

First, the function of STs and NEUs is significantly different. STs are enzymes transferring the SA from cystidine-5-monophospho-N–acetylneuraminic acid (CMP-Neu5Ac) to the terminal position of carbohydrate group of glycoproteins and glycolipids,[2,6,7,11,12] and in contrast, NEUs catalyze the hydrolysis of α-glycosidic bonds linking SA residues to carbohydrate groups of glycoproteins and glycolipids, which is the initial step in the degradation of these glycoconjugates.[4,5,13,14] The role of STs may be more constant, although STs can be further classified as four main classes based on their linkage specificities and acceptor substrates, including (1) the ST3Gal family (I to VI), adding α2,3-linking SA to a terminal galactose of N-, O-linked glycans and glycolipids; (2) the ST6Gal family (I to VI), adding α2,6-linking SA to galactose residues of N-glycans; (3) the ST6GalNAc family (I to III), adding α2,6-linking SA to terminal N-acetylgalactosamine (GalNAc) residues of glycoproteins and glycolipids; and finally, (4) the ST8Sia family (I to VI), catalyzing the addition of α2,8-linking SA to another SA residue in N- or O-glycans.[12] However, in mammals, there are four types of NEUs, including NEU-1 (in the lysosomes and involvement of exocytosis, immune response, phagocytosis, and elastic fiber assembly), NEU-2 (in the cytosol and plasma membrane and involvement of myoblast and neuronal differentiation), NEU-3 (in the plasma membrane, and involvement of neuronal differentiation, apoptosis, and adhesion), and NEU-4 (in the lysosomes or in the mitochondria and endoplasmic reticulum, and involvement of neuronal differentiation, apoptosis, and adhesion), but these four NEUs significantly differ from each other by their expression patterns, localization, and of most important their functions.[12,13] It is relatively interesting to find that both ST3Gal-1 and NEU-3 levels were increased in patients with RA,[10] since the former may add SA on the surface of monocytes but the latter may remove SA on the surface of monocytes, but then finally, the SA on the monocyte surface was increased, which supported the diverse function of sialidases (NEU) on the different cells, tissue, or organs.

Second, the hypersialylation might play an important role for many pathological processes.[12] For example, hypersialylation of the cancer cells contributes to cancer progression, metastases, and resistance of apoptosis or therapy.[6,7,11,12] There are three key mechanisms to describe the relationship between hypersialylation and cancer cells, including (a) an increased expression and/or aberrant activity of STs leading to increased sialylation of glycans or specific tumor-associated carbohydrate antigen; (b) increased substrate availability or overexpression of genes involved in SA biosynthesis; (c) differential expression of endogenous NEUs resulting in an increased sialylation of tumor cells.[13]

Third, the immune cells might be different from the cancer cells in the sialylation status. In our previous studies, we also found that blockage of α2,3-sialylation of natural killer (NK) cells might result in the decreased ability of migration and phagocytosis ability of NK cells in co-culture system with HeLa cells (cervical cancer cell lines).[5,6] It is rationale to suppose that, in the

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autoimmune diseases, activity of some immune cells might be activated. Therefore, it is not surprising to find that in Drs. Liou and Jang's current study, the level of cell surface SA expression of monocytes, B and T cells in patients with RA was increased.[10] However, we are wondering why another autoimmune disease, SLE, did not show the similar findings.[10] All supported that glycosylation (sialylation) change is more complicated than that we expected.

Finally, if the activity of STs of monocytes is correlated with disease activity of RA, and especially ST3Gal-1 was found in the current study, the ST3Gal-1 inhibitors might be valuable in the clinical application. Recently, a review summarized the recent advances and eight groups were proposed, including (a) SA analogs, (b) CMP-SA analogs, (c) cytidine analogs, (d) oligosaccharide derivatives, (e) aromatic compounds, (f) flavonoids, (g) lithocholic acid analogs, and (h) others.[12] However, none is specific to anti-ST3Gal-1. In our laboratory, the specific ST3Gal-1 inhibitor (Soyasapoin-1) has been developed and its efficacy and safety has been evaluated and confirmed in the vitro and animal models.[4–7,15,16] We look forward to learn much more research focusing on the field of glycobiology, because much evidence supported its value not only for the chronic illness but also for the cancer treatment.

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