Jamey D. Marth

Profile

My laboratory combines molecular, cellular, and physiological research to investigate the roles of mammalian glycans in biology and disease. Modern literature including the current widely used cell biology textbook by Alberts et al., states that glycans are one of the four fundamental components of cells, along with lipids, proteins and nucleic acids. All four of these macromolecules and structural components consist of a defined set of building blocks that are used to produce their diverse structural repertoires. The glycan repertoire, termed the glycome, consists of saccharides linked by glycosidic bonds to proteins, lipids, and other saccharides. Considering their abundance and diversity, relatively few laboratories incorporate them into an integrated research program. Because glycans are not directly encoded by the genome, defining their structure and function is more difficult and not amenable to template-based biology and its associated current high-throughput technologies. With combinations of genetic, biochemical and physiological approaches, including Cre-loxP conditional mutagenesis developed by this laboratory, the biological roles of protein glycosylation have been increasingly revealed. The functions ascribed to glycans discovered by this laboratory, span roles in apoptosis, autoimmune disease, the complications of sepsis, and as the appended revised R01 A1 proposal includes – the origins of diet- and obesity-associated diabetes. Studies over the past two decades indicate that glycans contribute to some of the most important missing pieces in the puzzles of disease, and their involvement presents opportunities for rational approaches to disease prevention and treatment. Our research spans the enzymes of glycosylation and the proteinaceous lectins that exist to decode the biological information contained in glycans. By doing so, we hope to achieve a more holistic and rigorous understanding of cell biology and the mechanisms that govern health and disease.

Glycosylation in the metabolic origins of common grievous disease

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Glycosyltransferases and glycosidases represent most of the enzymatic machinery that participates in determining the structural repertoires of glycans produced by cells and organisms. Changes in the glycome can be observed in both genetic and acquired disease states. While some genetic diseases have been linked directly to DNA sequence variation that then alters the enzymes of glycosylation, multiple common diseases and syndromes appear to originate from metabolic changes in glycosylation in the absence of detectable inherited genomic variation. From studies over the past two decades, this laboratory has identified environmental triggers that alter mammalian and human glycosylation, and which represent metabolic origins of common grievous disease. These metabolic factors include dietary stress and microbial interactions/infections with the host organism. The disease pathways induced by such metabolic processes include, for example, the pathogenesis of Type 2 diabetes in response to obesity, primary insulin resistance, and high levels of free fatty acids. In this disease pathway, an acquired change in glycosylation is responsible for disabling the first step of glycolysis among pancreatic beta cells, which then causes beta cell dysfunction that provokes disease onset. In another example, the altered metabolism of glycans has been found to determine the outcomes of infection among pathogens and their hosts bearing normal genomes. Examples of such microbial interactions have been identified among our studies of the common mammalian pathogens *Streptococcus pneumoniae* and *Salmonella typhimurium*. Infections by these bacteria cause metabolic changes in host glycans that are sensed by host receptor systems residing in various tissues. The outcomes of such interactions determine the course of disease, including the severity of host tissue damage and the frequencies of host survival. From these and other studies to be described, we are developing and combining high-throughput detection approaches to simultaneously interrogate the four macromolecules and structural components of cells, namely the nucleic acids, the proteins, the lipids, and the glycans. By observing both the inherited biological responses governed by the expression of genes and proteins, and the acquired biological responses governed by the metabolism of glycans and lipids, such combined studies may further reveal the origins and pathways of common mysterious diseases that arise from metabolic triggers. Almost all diseases originate from a combination of inherited and environmental factors that when considered together will be able to explain the roles of nature and nurture in disease pathogenesis.

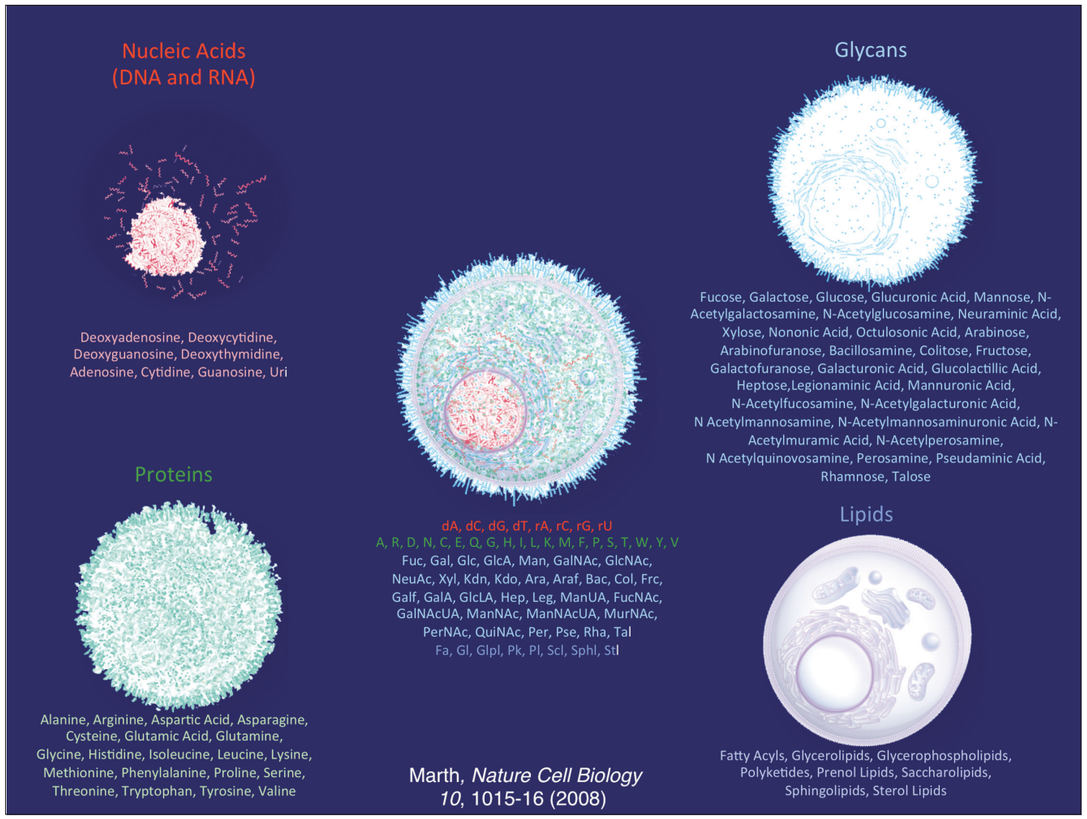

FIgure 1. The molecular building block of life.
We have further defined 70 basic building blocks of life in all cells, yet we can only see a small portion, less than half.…
By developing the means to interrogate and modulate all of these cellular components…our research at the CNM can address multiple grievous and mysterious diseases, many of which are escalating in the human population

References

1) Orban, P.C., Chui, D., and Marth, J.D. (1992). Tissue - and site-specific DNA recombination in transgenic mice. *Proc. Natl. Acad. Sci. USA* 89, 6861-6865.
2) Gu, H., Marth, J.D., Orban, P.C., Mossmann, H., and Rajewsky, K. (1994). Deletion of the DNA polymerase beta gene in T cells using tissue-specific gene targeting. *Science* 265, 103-106.
3) Hennet, T., Hagen, F.K., Tabak, L.A., and Marth, J.D. (1995). T cell-specific deletion of a polypeptide Nacetylgalactosaminyltransferasegene by site-directed recombination. *Proc. Natl. Acad. Sci. USA* 92, 12070-12074.
4) Chui, D., Oh-Eda, M., Liao, Y.F., Panneerselvam, K., Lal, A., Marek, K.W., Freeze, H.H., Moremen, K.W., Fukuda, M.N., and Marth, J.D. (1997). Alpha-mannosidase-II deficiency results in dyserythropoiesis and unveils an alternate pathway in oligosaccharide biosynthesis. *Cell* 90, 157-167.
5) Hennet, T., Chui, D., Paulson, J.C., and Marth, J.D. (1998). Immune regulation by the ST6Gal sialyltransferase. *Proc. Natl. Acad. Sci. USA* 95, 4504-4509.
6) Ellies, L.G., Tsuboi, S., Petryniak, B., Lowe, J.B., Fukuda, M., and Marth, J.D. (1998). Core 2 Oglycan biosynthesis distinguishes between selectin ligands essential for leukocyte homing and inflammation. *Immunity* 9, 881-890.
7) Priatel, J.J., Chui, D., Hiraoka, N., Simmons, C.J.T., Richardson, K.B., Page, D.M., Fukuda, M., Varki, N.M., and Marth, J.D. (2000). The ST3Gal-I sialyltransferase controls CD8+ T cell homeostasis by modulating O-glycan biosynthesis. *Immunity* 12, 273-283.
8) Shafi, R., Iyler, S.P.N., O'Donnell, N., Ellies, L.G., Marek, K.W., Chui, D., Hart, G.W., and Marth, J.D. (2000). The O-GlcNAc transferase gene resides on the X chromosome and is essential for embryonic stem cell viability and mouse ontogeny. *Proc. Natl. Acad. Sci. USA* 97, 5735-5739.
9) Chui, D., Sellakumar, G., Green, R.S., Sutton-Smith, M., McQuistan, T., Marek, K.W., Morris, H.R., Dell, A., and Marth, J.D. (2001). Genetic remodeling of protein glycosylation in vivo induces autoimmune disease. *Proc. Natl. Acad. Sci. USA* 98, 1142-1147.
10) Ellies, L.E., D. Ditto, D., Levy, G.G., Wahrenbock, M., Ginsburg, D., Varki, A., Le, D., and Marth, J.D. (2002). Sialyltransferase ST3Gal-IV operates as a dominant modifier of hemostasis by concealing asialoglycoprotein receptor ligands. *Proc. Natl. Acad.Sci. USA* 99, 10042-10047.
11) Ohtsubo, K., Takamatsu, S., Minowa, M.T., Yoshida, A., Takeuchi, M., and Marth, J.D. (2005). Dietary and genetic control of glucose transporter glycosylation promotes insulin secretion in suppressing diabetes. *Cell* 123, 1307-1321.
12) Grewal, P.K., Boton, M., Rameriz, K., Collins, B.E., Chui, D., Paulson, J.C., and Marth, J.D. (2006). ST6Gal-I restrains CD22-dependent antigen receptor endocytosis and Shp-1 recruitment in normal and pathogenic immune signaling. *Mol. Cell. Biol.* 26, 4970-4981.
13) Green, R.S., Stone, E.L., Tenno, M., Lehtonen, E., Farquhar, M.G., and Marth, J.D. (2007). Mammalian N-glycan branching protects against innate immune self-recognition and inflammation in autoimmune disease pathogenesis. *Immunity* 27, 308-320.
14) Grewal, P.K., Uchiyama, S., Ditto, D., Varki, N., Le, D.T., Nizet, V., and Marth, J.D. (2008). The Ashwell receptor mitigates the lethal coagulopathy of sepsis. *Nat. Med.*, 14, 648-655. NIHMSID: NIHMS183221
15) Ohtsubo, K., Chen, M.Z., Olefsky, J.M., and Marth, J.D. (2011). Pathway to diet- and obesity-associated diabetes through attenuation of pancreatic beta cell glycosylation and glucose transport. *Nat. Med.*, 17, 1067-1075.