

A sweet view of reproduction

In recent years, the advent of 'omics' has permitted large-scale molecular comparisons of cells, tissues, and secretions under different conditions. In reproductive medicine, ovarian and breast cancer, endometriosis, infertility, and failed implantation contribute significantly to the global burden of diseases. Much focus has been given to genomic markers used to generate molecular signatures of cells and organs, but more than 50% of expressed proteins are further modified by cotranscriptional and posttranscriptional events, which may not be reflected in altered gene expression profiles alone. The availability of newer secretomic technologies is aimed at recognizing diagnostic biomarkers in human body fluids in the hope of identifying disease markers. Much of the focus has been on proteomics, particularly with the recent advances in mass spectrometry instrumentation that have enabled identification and quantification of proteins abundance between normal and disease states.

The last two decades have also seen significant improvements in the feasibility of glycan (oligo- and polysaccharides attached to glycoconjugates such as glycolipids, glycoproteins, and proteoglycans) analyses based on mass spectrometry. Glycomic profiling allows both the monosaccharide composition analysis of tissue samples and the detailed profiling of different classes of glycans. It is now possible to gain important knowledge about the identity and abundance of glycoconjugates from even very limited biologic samples. As it turns out, all living cells are coated by a thick glycocalyx (sugar coat) consisting of complex oligo- and polysaccharides attached to glycoproteins and glycolipids. Some glycoproteins, such as mucins on epithelia (including endometrium), are 50% to 80% glycan by mass.

Unlike protein synthesis, glycosylation is not a template-driven process but rather results from sequential actions of cotranslationally and posttranslationally active enzymes in the endoplasmic reticulum and Golgi apparatus of cells. The same protein can have radically different biological effects based on the glycan modification that is added. Glycosylation plays an important role in diverse protein functions, communication between the cell and its environment, immune recognition and response, inflammation, and tissue and organ development (1). Changes in glycoprotein moieties result in altered biological function and have been observed in cancer, diabetes, rheumatoid arthritis, and cardiovascular-immunologic-congenital-infectious disorders. In women with ovarian cancer, a decrease in galactosylation of IgG and an increase in sialyl Lewis X, with an increased half-life and decreased apoptosis rate of cells, have been seen (2).

Glycomic profiling allows both the monosaccharide composition analysis of tissue samples and the detailed profiling of different classes of glycans (N- and O-glycans) released from the proteins to which they are attached as well as glycosaminoglycans and glycolipids in vivo. In breast cancer, certain N-glycans have been found as highly probable biomarkers of the disease, and alterations in the plasma N-glycome in patients with endometriosis suggests a potential marker of endometriosis.

The surface of gametes is no exception. Sperm have a particularly thick glycocalyx, and oocytes have a polysaccha-

ride (hyaluronic acid) matrix that surrounds the egg and its complex mesh of zona pellucida glycoprotein heteropolymers, which bear species-specific glycans (3). Furthermore, seminal fluid and uterine secretions contain large amounts of secreted glycoconjugates such as glycodelin, which carry sex-specific modifications. Moreover, the immune environment of the female reproductive tract includes antibodies targeting glycans on sperm surface glycoproteins, such as CD52 with sperm-specific glycans. Sperm also achieve strong immune evasion by being coated with highly sialylated glycopeptides such as β -defensin-126 (4). Glycoproteins secreted by the female also vary across the reproductive cycle (e.g., cervical mucin) and along the reproductive tract; for example, glycodelin has different glycoforms in the uterus, the oviduct, and the cumulus. Furthermore, mammalian sperm carry neuraminidases that modify their sialic acids during capacitation, and inhibition of their activity in vitro can compromise capacitation and sperm-zona pellucida binding in mice (5).

Given the important roles of glycoconjugates for many biological recognition processes, including fertilization, development, inflammation, and immunity, the inclusion of glyco-biological analyses (glycomics) will be crucial to provide an integrated view combined with genomic, proteomic, metabolomic, and lipidomics (all the -omics) and to improve our understanding of key determinants in human reproduction.

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