Commentary

Oligosaccharide signals: From plant defense to parasite offense

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For over 40 years specific structural features of complex carbohydrate components of glycoproteins have been studied as recognition signals for various biochemical and physiological processes in animals and yeast, such as glycoprotein turnover, cell–cell adhesion, cytolysis, and hormone action, as examples (1). However, roles for oligosaccharides in modulating interactions of pathogens and pests with their hosts have been, to date, a unique feature of plants (2, 3). Oligosaccharide signals in plants, whether for regulating defense, environmental, or developmental responses, have been cumulatively given the name “oligosaccharins” (2). The article by Velupillai and Harn (4) in this issue describes the first example in which a defined oligosaccharide, lacto-*N*-fucopentaose III (LNFP-III) (by definition an “oligosaccharin”), derived from a surface antigen of the eggs of a parasite, *Schistosoma mansoni*, plays a signaling role in the interaction of parasite with its animal host, thereby regulating the immune responses of the host. This is the first report of a ligand, a complex carbohydrate, that regulates the elaboration of a cytokine.

Parasites invade virtually every organ of their animal hosts, while evading nearly all of the host's immune defense responses. Parasites create their own environments in tissues and lay eggs where the worms hatch and thrive. How these parasites evade the immune systems of their hosts is a question important not only to understanding and treating parasite infections but also to other disease states in which the immune system is disabled or evaded.

The most effective host defense against schistosome parasites is considered to be the cell-mediated immune system, in which macrophages, activated in response to the parasite, destroy the worms. Worms that survive lay eggs that trigger an alteration of the lymphoid T-cell responses, shifting the immunity from cell-mediated to antibody-mediated, which is ineffective in combating the infection (5). T cells contain several subsets that function in lymphokine secretions. Th1 cells produce cytokines, such as interferon γ , that regulate delayed-type hypersensitivity responses, and Th2 cells produce other sets of cytokines, including interleukin 10, that in-

duce B-cell activation and differentiation. Th1 and Th2 cells can down-regulate each other because interferon γ inhibits Th2 proliferation and interleukin 10 inhibits synthesis of Th1 cytokines (5, 6). Velupillai and Harn (4) report that the schistosome cell-surface egg oligosaccharide triggers the production of a specific subset of B cells that produce cytokines known to down-regulate Th1 responses. Thus, their report provides the first evidence for elaboration of a cytokine in response to an oligosaccharide signal.

Oligosaccharides as signals involved in defensive responses were first identified in plants in the early 1970s by Albersheim and his associates (2, 7); they were seeking the chemical signals derived from invading fungal pathogens that induced the synthesis of antibiotics (called “phytoalexins”) in host plants as a defense response against the pathogens. Within a few years, a glucan heptasaccharide composed of β -1,3 and β -1,6 linkages was isolated from the pathogenic fungi *Phytophthora megasperma*, and its absolute structure was determined (8).

Other oligosaccharides derived from the cell walls of pathogenic fungi were subsequently isolated and characterized that were also potent signals for activating plant defensive responses (9). Chitin oligosaccharides (β -1,4-acetyl glucosamine linkages) and chitosan oligosaccharides (β -1,4-*N*-acetyl glucosamine linkages), both derived from fungal cell walls, were found to be potent signals for the synthesis of phytoalexins and other defensive chemicals in plant tissues. The release of β -glucans, chitin, and chitosan oligosaccharides from fungal cell walls is mediated by β -glucanases and chitinases, present in the host plants (3). These enzymes are usually present at low levels in plants but can be induced to much higher levels in a feedback loop in response to the fungal-cell-wall oligosaccharide fragments.

The full scope and complexity of the signaling processes during the interaction of pathogens and pests with plants is not well understood, but other types of oligosaccharides, such as oligogalacturonides (2, 3) produced from the plant cell wall by enzymes secreted by pathogens, are also known to play key roles in signaling defensive responses against both

pathogens and insect pests. Pathogenic fungi commonly release endopeptolytic enzymes to loosen the plant cell wall to facilitate infection. The resulting plant-cell-wall-derived oligosaccharide fragments, which are produced in mass, can also act as signals to activate defensive responses in nearby cells. Thus, the outermost components of both the attacking fungi and the plant contain oligosaccharide structures that can act as signals to activate the inducible arsenal of defensive chemicals of plants.

Velupillai and Harn (4), in investigating the shift of the lymphoid T-cell response from Th1 to Th2 cells that occurs during schistosomiasis, with an interest in other disease states as well, had found earlier that the glycoproteins of the outer envelope of schistosome eggs contain two immunoreactive oligosaccharides, LNFP-III and the nonfucosylated homologue lacto-*N*-neotetraose. They noted that LNFP-III contained the Lewis^x trisaccharide structure, a structure present in ligands of proteins previously associated with lymphocyte function. LNFP-III was investigated as a signal and found to stimulate a B-cell-enriched population of spleen cells to produce large amounts of interleukin 10 and prostaglandin E₂, which down-regulate Th1 responses, thereby suppressing cell-mediated immunity. The fundamental similarities between the parasite signaling for cytokine regulation strongly suggest that oligosaccharide ligands may operate in other disease states, such as human immunodeficiency virus infections and malignant carcinomas.

The finding of a commonality of defensive strategies within plant–pest and animal–pest interactions involving oligosaccharide signals adds to the expanding list of analogies between plant and animal signaling systems. Only recently the first polypeptide hormone was isolated and characterized from a plant (10) and, similar to animal polypeptide hormones, it was found to be derived from a prohormone precursor (11). A prostaglandin analog, jasmonic acid, has also been identified recently in plants as a common intracellular signal that regulates synthesis of a variety of developmental and environmental responses (12, 13). Whether any or all of these signaling analogies among animals and plants are from convergent or

divergent origins is unknown, but the fundamental knowledge learned from these signaling pathways will be important in furthering our understanding of how various plants and animals compete and survive in a hostile world and will perhaps provide additional approaches to several of the world's most pressing medical problems.

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