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Golgi Apparatus: Influence on Cell Surfaces

A role in the assembly of macromolecules makes the organelle a determinant of cell function.

W. Gordon Whaley, Marianne Dauwalder, Joyce E. Kephart

There is a growing awareness that many cellular functions are directly influenced or "controlled" by macromolecules "outside" the cell, either as components of the plasma membrane, or as cell surface–associated materials, or as components of intercellular matrices (*1*). Many of these macromolecules have now been shown to have carbohydrate moieties (for example, glycoproteins, mucopolysaccharides, proteoglycans, and some glycolipids are involved). The Golgi apparatus functions both in the synthesis or assembly of some of these carbohydrate-containing materials and in their transport to the cell surface as part of the secretory process. The apparatus thus provides a focal point to which we may relate many of the findings regarding cell surface–mediated phenomena that come from numerous separate fields.

Much attention has been directed to the specificity of proteins and the manner in which this specificity is genetically determined by nucleic acid coding of amino acid sequences. Nonetheless, the fact that there is a high degree of genetically controlled specificity in certain carbohydrate groups has also been known for many years from various studies with microorganisms, from blood group studies, and from immunochemical studies (*2*). Carbohydrate-containing materials found generally at the surface of cells (*3, 4*) have now been implicated in fundamental aspects of cellular function such as recognition, motility, and association (*4–6*). For example, specific carbohydrate groups are responsible for recognition and adhesion between mating types in many unicellular organisms (*7*) and may be responsible for recognition by gametes of higher organisms (*8*). They are also involved in recognition and cell-specific adhesion in the structuring of multicellular forms, for example, in the species-specific aggregation of sponge cells, in the histiotypic association of embryonic cells, and in the formation of cell contacts in *Dictyostelium* (*9*). Alteration of carbohydrate-containing surface materials brought about by virally induced cell transformation may explain several characteristics of virus transformed cells such a cell fusion, selective agglutination, and the release of cells from contact inhibition (*4, 5, 10*), and may relate to the development of malignancy in general (*4, 5, 11*). Antigenic specificity characteristics of glycoproteins with blood group activity are determined by particular sugar groups added sequentially to a polypeptide moiety (*12*). In many instances, the particular characteristics of surface materials can be correlated with sugar sequences that include galactose, fucose, and sialic acid.

The surface specificity of cells provides selectivity for materials taken into the cell both by passage through the membrane and by endocytic phenomena. In instances of the intake of materials by endocytosis, surface specificities may determine the fate of the engulfed material, for example, whether and to what extent it is degraded in the lysosomal system (*13*). Removal of segments of plasma membrane with associated material during endocytosis can be compensated for by incorporation of secretory vesicle membranes. Such "new" membrane segments may carry different specificities into the plasma membrane (*14, 15*). The cycling and recycling of surface materials may provide for the changing specificities in informational content essential for the control of differentiation and development.

Both at the cellular and supracellular levels various developmental phenomena may be guided by cell-to-cell and cell-to-environment interactions in which carbohydrate-containing materials act as determinants. It has been proposed that "informational potential" of such materials located at the cell surface could explain characteristics of cell movement, morphogenesis, and adaptability to environmental stimuli during embryogenesis (*16*). Similar materials have been implicated in various mor-

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phogenetic aspects of epithelial-mesenchymal interactions (*17*). Particular attention has been called to the role of carbohydrate-containing intercellular materials in bringing about or stabilizing cell differentiation during embryonic induction and tissue morphogenesis (*18*).

The functioning of highly differentiated cells also involves special surface characteristics. The mucopolysaccharide coating of the brush border of intestinal cells is the site of the digestive enzymes invertase and maltase, may be the location of antigenic sites or specific receptor sites (such as for the vitamin B_{12}–intrinsic factor complex), and may also serve as a filtration gel influencing the absorption of various ions or molecules (*19*). The glycoprotein nature of the mucus coat in the stomach may be specifically related to characteristics of ion permeability, which could cyclically control the release of gastrin and its subsequent stimulation of gastric acid secretion (*20*). The controlled modulation of intercellular hydration and ion distribution and exchange by carbohydrate-containing materials may be of particular importance in many aspects of neural functioning (*21*).

Throughout the whole period of studies of the coding of polypeptide chains by nucleic acids there has remained the question of whether this mechanism provided extensive enough biological information in essential patterns of distribution to guide all the activities in which the cell becomes involved. The concept that has emerged is that informational capacities inherent in the structure of some proteins can be greatly enhanced by the addition of particular carbohydrate chains that may confer different types of specificity or allow for a greater range or variability in specificity. It suggests further that many carbohydrate-containing materials when exteriorized from the cell have particular "informational" characteristics responsible for influencing a wide range of cellular activities (*22*).

The current emphasis on the importance of materials "outside" the cell directs attention to the role of the Golgi apparatus, an organelle which has long been recognized to be centrally involved in secretion (*23*). During secretion the membranes of the Golgi apparatus are specialized for the assembly of secretory materials and for the formation of membrane-bounded vesicles in which masses of material are transported to the cell surface. Recent evidence suggests that the Golgi apparatus may also act in the synthesis of certain polysaccharides and in the synthesis or attachment of the carbohydrate side chains of glycoproteins (or possibly glycolipids). These macromolecules are components of various materials including mucins, intercellular matrix materials of both plants and animals, and surface-associated materials of cells not normally considered "secretory." Various staining procedures generally indicative of polysaccharides show localization in the Golgi apparatus or its derived vesicles and comparable localization at the cell surface (*3, 4, 24*). Radioautographic techniques have shown the rapid uptake of several labeled sugars by the Golgi apparatus, without any seeming prior passage through the endoplasmic reticulum, and their subsequent transport and secretion (*6, 25*). Biochemical analyses of Golgi apparatus–rich fractions have consistently shown relatively high values of glycosyl (particularly galactosyl) transferases (*26*).

Detailed data on the synthesis of several glycoproteins (*27*) [for example, thyroglobulin (*28*); immunoglobulins (*29*); and some components of the connective tissue matrix (*30*)] suggest that the Golgi apparatus functions as part of an "assembly line" along which sugar groups are sequentially added to a protein moiety. Synthesis of the protein is restricted to the ribosomes in association with the endoplasmic reticulum, whereas sugar groups are added at different sites in the cell. The sugar groups closely linked to the polypeptide chain (often including glucosamine and mannose) are added either as the presumptive polypeptide chains come off the ribosomes or in the endoplasmic reticulum while the more terminal sugars (often including galactose, fucose, and sialic acid) appear to be added later in the Golgi apparatus. The secretory products may be further modified in Golgi apparatus–derived vesicles during transport and at the plasma membrane.

The evidence is thus consistent with the concept that the Golgi apparatus plays a large part in determining certain of the characteristics of cell surface–associated materials through its ability perhaps to synthesize and certainly to link carbohydrate groups to proteins to form informationally rich macromolecules. The arrangement of the more terminal sugar groups must be a primary factor in determining the information potential of these materials either because of the specificities of these groups themselves or because they may have to be removed to make other information in the macromolecule available. In addition, the incorporation of vesicles produced by the Golgi apparatus in discrete regions of the cell membrane may provide for a particular spatial distribution of specificity characteristics in the surface-associated materials. This differential localization of specific carbohydrate groups, as seen for example in the positioning of the H-2 antigens in mouse lymphocytes and thymocytes (*31*), must be of importance in affecting cellular phenomena.

The Golgi apparatus can be viewed as the membrane-bounded compartment of the cell where enzymes involved in the synthesis of particular carbohydrate groups are present, have the necessary spatial organization, or are active. Currently, particular emphasis can be placed on the synthesis of the more terminal sugar sequences in the assembly of various materials as they may be a critical part of determining the information potential. While the site of the initial attachment of sugars to the polypeptide chain is determined in part by information inherent in the amino acid sequence itself, the subsequent stepwise addition of specific sugars appears to require further genetic control and to be brought about by the activities of specific enzymes compartmentalized in the Golgi apparatus. Part of the Golgi apparatus function appears to be the assembly of membranes that have specific characteristics. This differentiated membrane seems to provide additional discrete sites for the genetically controlled assembly of specificity groups in macromolecules between the original structuring of the polypeptides and the cell surface where these "informational macromolecules" determine cellular association and development. As a result, the characteristics of the plasma membrane and its associated surface materials may be in part dependent on membrane specialization in the Golgi apparatus.

The genetic control of specificities in surface carbohydrates is amply demonstrated by data on the various materials having specific blood group characteristics (*12*). Such control may explain phylogenetic aspects of connective tissue matrix components (*32*), the patterns of connective tissue glycoproteins from monozygotic and dizy-

gotic twins (*33*), and is clearly implicated in abnormal development of cartilage in a chondrodystrophic mutant in mice (*34*). Evidence concerning the functioning of the Golgi apparatus thus implies a relationship between the genome and its regulators, the Golgi apparatus, the cell surface, and the ultimate pattern of development and functioning. That many different carbohydrate moieties are unerringly synthesized in the absence of individual informational templates suggests a high degree of both specificity and organization of the individual glycosyltransferases. In addition to enzyme specificity, it seems likely that the specialization of the Golgi apparatus membranes (or segments of membrane) influences or determines the association with them of enzymes or enzyme groups. Obscure questions of "membrane flow" are also involved in instances where the final complex structuring of the chains is dependent on the sequential addition of particular sugars in the endoplasmic reticulum and in the Golgi apparatus. Among these questions are not only ones concerning specialization and transport of membrane but also ones having to do with the regulation of these activities.

The cyclic and developmental differentiation of the Golgi apparatus when considered as part of a process transferring membrane and information-bearing materials to the surface of the cell could well account for essential changes in surface characteristics which may have prime importance in the progressive determination of morphogenetic differentiation and in integrated aspects of multicellular functioning.

These activities give the Golgi apparatus a major role in the anabolic functioning of the cell. The organelle, however, also plays a substantial part in catabolic functioning through the formation of membrane-bounded vesicles containing lysosomal enzymes (*35*). The membranes of these lysosomal vesicles have the capacity to fuse either with endocytic vesicles derived from the plasma membrane, or in certain cases, with the plasma membrane itself (*14*, *36*). The specificity of this fusion may be related to membrane characteristics developed in the Golgi apparatus since both regions of the plasma membrane and the lysosomal vesicles have their origin in this organelle. In the case of fusion with endocytic vesicles the lysosomal enzymes act in the degradation (or partial degradation) of surface materials brought back into the cell while the "secretion" of lysosomal enzymes results in the degradation of intercellular matrix materials.

The Golgi apparatus may thus function in interrelated cycles of both the buildup and the breakdown of extracellular materials. The overall balance of cellular activity, the integrity of various cellular processes, and even the functional coordination between different tissues may depend on sequentially or temporally controlled alternations (or both) between parts of this cycle (*37*). In both phases of the cycle factors of membrane recognition and transformation seem to be in considerable measure developed in the Golgi apparatus. We can thus look upon the Golgi apparatus as a key organelle in the regulation of normal development and functioning (*38*) with respect both to its involvement in the dynamic balance of cellular anabolism and catabolism and to its function in the enhancement of the biological information content of surface-associated materials. It seems most likely that dysfunction and degeneration could involve modifications in the activities of this organelle.

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Factors Contributing to Current Distress in the Academic Community

The growth of the NIH extramural program from 1960 to 1970 is analyzed.

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An analysis of the fiscal history of the National Institutes of Health (NIH) through the 1960's was undertaken in an attempt to explain the disproportion between the recent variations in NIH funds for biomedical research and the stress and perturbation currently experienced throughout the academic community.

The institutes and research divisions of NIH (later abbreviated I/RD) obligated more funds for the support of research each year of the decade until fiscal year 1970, when obligations declined by 5 percent, and an increase in appropriations for the next fiscal year has permitted obligations in excess of those for 1970 by about 15 percent. The distress of the academic community, however, is due to quite tangible constraints and dislocations imposed by three principal factors: sudden deceleration of program growth; inflation, sometimes exceptional in the biomedical sphere; and marked variations in the funding of NIH components, each receiving separate appropriations from the Congress.

During the decade, there have been a number of organizational changes, such as the creation of new institutes and divisions—National Institute of General Medical Sciences (NIGMS), Division of Research Resources (DRR), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), National Eye Institute (NEI), and Division of Regional Medical Programs (DRMP)—both newly established and as a result of internal reorganization; the separation of components from NIH—DRMP and National Institute of Mental Health (NIMH); and the addition of new components—Bureau of Health Manpower Education (BHME) and National Library of Medicine (NLM). All fiscal data included in this report have been adjusted for these changes to ensure consistency and compatibility.

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Budgetary History

The NIH budget from fiscal year 1960 through 1970 is presented in the aggregate, with several subsets that are of interest (Table 1).

1) Many of the tabulated data are derived directly from budget activity schedules and are self-explanatory: regular research grants, special program grants, general research support grants, research contracts, training grants, fellowships, and research facilities construction grants.

2) The total of these obligations—extramural program (I/RD)—is a comprehensive measure of current operating support to grantee institutions and of long-range capital investment in their people (through training awards) and their space (through construction grants).

3) Obligations for academic science include research, training, and facilities awards to academic institutions.

4) A subset of these—awards to medical schools by the institutes and research divisions of the NIH—is available only from fiscal year 1967 to date. Prior to that time, the series included awards to medical schools from NIH as well as the current components of the NIH. The formidable clerical task of stripping out the former data from the time series has not been completed. The combined NIH-NIMH data from fiscal 1960 to 1970 is still of consider-