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The Golgi is a Measuring Cup

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Abstract

The relation of organelle size to cellular function is a basic question in cell biology about which almost nothing is known. Reporting in *Developmental Cell*, Ferrero et al. show that the size and topology of the Golgi apparatus determines the size and functionality of a medically important secretory granule.

Organelles are not just amorphous sacs of membrane but rather have highly reproducible and beautiful structures. The Golgi is a particularly dramatic example with its complex topology of interconnected stacks of membranous cisternae. But while cell biologists have marveled at the beauty of organelle structure for over a century, we know surprisingly little about how the geometry of organelles affects their function. The structural complexity of the Golgi has often been discussed in terms of how it might regulate sequential processing events of secreted proteins, much as a conveyor belt regulates sequential addition of parts on the assembly line of a car factory. Now, a quantitative analysis of secretory particle size has shown that both the size and topology of the Golgi influence the size of secreted particles, with corresponding influence on secretory function, showing that the Golgi does not just determine modifications of proteins but also regulates their assembly into multimeric objects prior to secretion. The Golgi is thus not only an assembly line, but also a measuring cup.

The relation between the size of Golgi cisternae and the size of secreted particles has been extensively studied in a somewhat unusual model system: algal scales [Melkonian et al., 1991]. Scales are glycoprotein and polysaccharide-containing particles that coat the cell body or flagella of different algal species. These scales range in size from approximately 50 nm for the flagella scales of *Scherfellia dubia* to 1 – 2 μm for the body scales of *Pleurochrysis scherffelii*. Regardless of their size, individual scales form within individual Golgi cisterna. Because the scales can be orders of magnitude larger than the vesicles that had been proposed to mediate trafficking between cisternae in the Golgi stack, algal scales were viewed as strong support for a cisternal maturation model of Golgi trafficking. This model postulates that individual cisternae, together with their cargo, undergo a series of maturation steps as they progress from one end of the Golgi stack to the other, as opposed to

the alternative model in which cargo proteins are shuttled from one cisterna of the stack to the next in small vesicles[Becker et al., 1995]. Studies of scale biogenesis focused on the question of how the Golgi cisternae were able to accommodate the large size of the scales, and tended to view the cisternae as passive containers whose only job was to be large enough to hold the scale that was self-assembling inside them.

In this issue of *Developmental Cell*, Ferraro and colleagues (2014) analyze the relation between Golgi size and the size of a different secreted particle, the Weibel-Palade Body (WPB). The WPB is a secretory granule produced by endothelial cells that contains the glycoprotein Von Willebrand Factor (VWF). Like the body scales of *P. scherffelii*, a single WPB can be more than one micron long. When the endothelium is injured, endothelial cells secrete WPB granules into the bloodstream, where they unwind long strings of VWF that serve as tethers to capture platelets [reviewed in De Ceunynck et al., 2013]. The maximum length of the VWF string that can be unfurled is proportional to the volume of the WPB, just as the length of kitchen twine is proportional to the volume of the ball of twine. We thus would expect that endothelial cells have evolved to contain size control systems for WPBs to ensure the WVF strings are the right length to capture platelets.

When Ferraro et al. (2014) measured the lengths of a large number of WPBs in human vascular endothelial cells, they found that the length distribution strongly favored lengths that were exact multiples of 500 nm. This observation suggested an underlying quantal nature of WPB assembly, in which large WPBs are built up by concatenation of multiple 500 nm precursors. The image of a WPB as an array of smaller subunits sparked the imagination of the authors, who recognized that the vertebrate Golgi itself shares this type of organization. Unlike most other eukaryotes, whose Golgi apparati are composed of one or more separate stacks of cisternae, vertebrate Golgi often form a more complex architecture in which several cisternal stacks (terms "mini-stacks") will associate side by side, connected by tubular connections. Ferraro et al. (2014) hypothesized that the quanta of WPB assembly corresponded to units of WPB assembled in different mini-stacks, and the array of such quanta in the final WPB corresponded to the array of mini-stacks in the Golgi apparatus that produced it. The beauty of this hypothesis is that it can be tested using molecular perturbations that change the size of mini-stacks and their connectivity. Changing mini-stack size led to a corresponding change in the size of the quanta. Eliminating the connectivity between mini-stacks led to production of much smaller WPBsthat corresponded to single quanta. Importantly, perturbations which altered WPB size also affected the length of the VWF strings, showing that the role of the Golgi in dictating WPB size is ultimately important for proper cell function.

The authors propose that WPB size control results from two interacting influences: the size of quanta is set by the size of the individual cisternae in a mini-stack, and the number of quanta that are combined to produce the final WPB is set by the number of mini-stacks interacting in the Golgi. In this model, the mechanism that determines the size of the Golgi cisternae plays a pivotal role by setting the size of the WPB quanta. Ferraro et al. (2014) then tested whether the quantity of VWF produced in the cell might dictate cisternal size. When the authors reduced VWF expression, the size of WPB quanta was not changed, ruling out this possibility. There must thus be some size control system regulating cisternal

dimensions independently of the quantity of secreted protein. The size of cisterna appears to be regulated by the kinetics of membrane trafficking through the Golgi [Bevis et al., 2002; Bhave et al., 2014].

Although WPB secretion by endothelial cells is a case of a specialized organelle within a particular cell types, we could expect the Golgi to play similar roles in any secretory cell. With this in mind, it would, for example, be interesting to know whether alterations in Golgi stack connectivity can influence the thickness of secreted mucus layers in the airway. Clearly, the present demonstration is just one step towards understanding the functional ramifications of organelle size and topology in secretory cells.

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